NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

OREXO AB and OREXO US, INC., Plaintiffs/Counterclaim Defendants, v. SUN PHARMACEUTICAL INDUSTRIES LIMITED, SUN PHARMA GLOBAL FZE, SUN PHARMA GLOBAL, INC., and SUN PHARMACEUTICAL INDUSTRIES, INC., Defendants/Counterclaim Plaintiffs.	Civil Action No. 3:20-cv-12588 (GC) (DEA) (consolidated) **OPINION** [redacted]

CASTNER, District Judge

THIS MATTER comes before the Court upon a Complaint for patent infringement brought by Plaintiffs Orexo AB and Orexo US, Inc. (collectively, "Orexo" or "Plaintiffs") against Defendants Sun Pharmaceutical Industries Limited, Sun Pharma Global FZE, Sun Pharma Global, Inc., and Sun Pharmaceutical Industries, Inc. (collectively, "Sun" or "Defendants") arising from Sun's filing of Abbreviated New Drug Application ("Sun's ANDA") No. 214737 with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Orexo's Zubsolv®, a drug approved for the treatment of opioid dependence. (*See generally* ECF No. 1.) Zubsolv®, is covered by U.S. Patent Nos. 9,439,900 ("the '900 patent") and 11,020,387 ("the '387 patent"), which, among other patents, are listed for Zubsolv®, in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). (*See, e.g.*, ECF No. 341 ¶¶ 28, 40.) The '900 and '387 patents are asserted in

this case (the "asserted patents"). (ECF No. 352.) U.S. Patent No. 8,940,330 ("the '330 patent") is in the same family as the asserted patents, and all three patents share substantially the same specification. (Davies Tr. 453:17-21.)

Before the Court are the issues of infringement and validity of the asserted patents, including Orexo's two oral motions under Federal Rule of Civil Procedure ("Rule") 52(c) on both the invalidity and infringement issues. (Tr. 964:16-21, 1094:19-24). Specifically, Orexo asserts the following claims: claims 2 and 16 of the '900 patent; and claims 6 and 13 of the '387 patent (collectively, the "asserted claims"). (ECF No. 341 ¶¶ 29, 41; *see also* ECF No. 351 at 1-2.) This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Rule 52(a) following a bench trial. The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified, and a thorough review of all of the evidence admitted at trial as well as the parties' post-trial briefing.

For the reasons set forth below, and for good cause shown, the Court finds that Sun's ANDA Products **INFRINGE** on the asserted patents and that the asserted patents are **VALID**.[1]

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[1] Plaintiffs orally moved under Rule 52(c) on both the infringement and invalidity issues. (Tr. 964:16-21; 1094:19-24; 1095:5-9.) Pursuant to Rule 52(c):

> [I]f a party has been fully heard on an issue during a nonjury trial and the court finds against the party on that issue, the court may enter judgment against the party on a claim or defense that, under the controlling law, can be maintained or defeated only with a favorable finding on that issue. The court may, however, decline to render any judgment until the close of the evidence. A judgment on partial findings must be supported by findings of fact and conclusions of law as required by Rule 52(a).

During trial, the Court reserved on both of Plaintiffs Rule 52(c) Motions. For the reasons set forth in this Opinion, Plaintiffs' Oral Motions under Rule 52(c) are **GRANTED**.

I. BACKGROUND

A. Parties

Orexo is a pharmaceutical company that manufacturers Zubsolv®, a drug used to treat opioid dependence. (DeLuca Tr. 84:18-23, 85:26-86:10.) Orexo AB is based in Sweden and Orexo US, Inc. is based in Morristown, New Jersey. (*Id*. at 85:9-13.) Orexo specializes in innovative pharmaceuticals that focus on mental health and substance use disorders. (*Id*. at 84:18-23.) Orexo is identified as the assignee of the asserted patents. (JTX-0003.0001, JTX-0005.0001.)

Sun is one of the largest generic pharmaceutical companies in the world. (Singh Tr. 777:2-6.) Sun's corporate office is based in Princeton, New Jersey. (*Id.* at 777:13-15) This case is a patent litigation stemming from Sun's ANDA for a generic version of Orexo's brand product, Zubsolv®. (ECF No. 341 ¶¶ 1, 14, 19-20.)

B. Suboxone®

In 2002, the FDA approved the use of Suboxone® tablets for the treatment of opioid dependence. (Crowley Tr. 1028:14-24; DTX-0027.0001, 0002, 0007.) Suboxone® was a sublingual tablet containing 2 milligrams ("mg") of buprenorphine[2] with .5 mg of naloxone[3]. (Crowley Tr. 1028:16-24; DTX-0027.0001, 0002, 0007.) Suboxone® also included inactive ingredients, including citric acid and sodium citrate. (DTX-0027.0001, 0002, 0007.) Following its approval in 2002, Suboxone® tablets became the "gold standard treatment for opiate dependence." (Crowley Tr. 1029:4-7.)

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[2] Buprenorphine is an opioid substitute used to treat opioid addiction and abuse. (*See* DeLuca Tr. 94:1-7.)

[3] Naloxone, an opioid abuse deterrent, is often combined with buprenorphine to prevent abuse. (DeLuca Tr. 94:8-11 (stating "If someone were to dissolve the tablet, and try to inject it, [naloxone] deters that abuse."); Sumner Tr. 272:3-6 (stating "the whole purpose of having naloxone in the product is to deter intravenous abuse.").)

However, as of 2011, there were approximately 4.3 million opioid addicts around the world, and the "diversion and illicit use of Suboxone [was] frequently [] reported." (JTX-0001.0013.) Additionally, Suboxone® was reported to have several significant limitations including insufficient bioavailability, poor disintegration, dissolution, and taste, and a gritty mouthfeel. (*Id.*; Fischer Tr. 118:19-119:3; Sumner Tr. 249:24-250:17, 252:18-25.) Suboxone® film was a new dosage form of the same buprenorphine and naloxone active ingredients intended to improve upon the shortcomings of Suboxone® tablets, but like the tablets, Suboxone® film has limited bioavailability and dissolves slowly. (Forrest Tr. 882:25-883:15; DeLuca Tr. 94:20-26; Sumner Tr. 256:23-257:10; JTX-0001.0013.) As such, a clinical need developed for "an abuse-resistant product for use in opioid addiction substitution therapy" with "increase[ed] [] bioavailability of buprenorphine" such that "it might be possible to reduce the amount of [buprenorphine], giving rise to less opioid in the formulation and so reducing the amount available for injection if diverted by way of intravenous abuse." (JTX-0001.0013.)

C. Zubsolv®

Orexo is the New Drug Application ("NDA") holder and manufacturer of Zubsolv®. (ECF No. 341 ¶ 14.) Zubsolv® was approved for the treatment of opioid dependence in 2013. (DeLuca Tr. 97:19-21; Sumner Tr. 270:1-3.) Andreas Fischer was the formulator responsible for Zubsolv® and he was tasked with preparing a formulation that improved the bioavailability of Suboxone®. (Fischer Tr. 173:22-25.) Fischer considered the following design choices related to Zubsolv®: (1) dosage form and route of administration; (2) ingredients (both active and inactive); (3) the arrangement of the ingredients; and (4) the formulation method to obtain the arrangement. (*Id.* at 119:19-120:12.) Mr. Fischer used a sublingual tablet for Zubsolv®, which is administered under the tongue. (*Id.* at 120:13-122:5; JTX-0001.0017.) He used buprenorphine and naloxone as the

two active pharmaceutical ingredients ("APIs") as well as a number of inactive ingredients. (Fischer Tr. 122:6-22; JTX-0001.0014.) Mr. Fischer used citric acid, a weak acid, which can be used to lower pH and facilitate dissolution of an opioid; croscarmellose sodium to accelerate the tablets disintegration when exposed to saliva; and carrier particles, such as mannitol and lactose, which is a large particle that has the ability to carry smaller particles, such as buprenorphine, on its surface. (Fischer Tr. 125:21-129:16, 129:24-130:4-7.)

There is no dispute the patents for Zubsolv® were issued because Mr. Fischer's formulation of Zubsolv® "unexpected[ly], [and] significantly improved" bioavailability compared to the prior-art Suboxone®. (JTX-0001, JTX-0006.0944.) In fact, the Patent Examiner stated that Orexo: "persuasively demonstrated that the instant tablet exhibits unexpectedly superior sublingual buprenorphine bioavailability due to the ingredients as well as the structural characteristics recited in the instant claims." (JTX-0011.171.) The separateness of the buprenorphine microparticles and weak acid particles promotes a "pH-timing effect." (Davies Tr. 575:15-21.) Saliva surrounds and quickly dissolves the separate weak-acid particles, which causes pH to be lowered by "about .05 to 5 pH units" for a short period, after which the original pH is restored, "resulting in improved and/or more rapid dissolution of microparticles of buprenorphine." (JTX-0001.0019-0020.)

With respect to the arrangement of the ingredients, Mr. Fischer used an ordered mixture in Zubsolv®. (Fischer Tr. 150:10-14.) Ordered mixtures are made up of ordered units, in which small particles associate with large particles and the individual particles retain their identity. (*Id.* at 130:25-131:17, 123:12-19; JTX-0001.0015-0016; Davies Tr. 461:17-462:21.) Composite mixtures, by contrast, dissolve together and the ingredients comingle together in the same particle and do not retain their identities. (Fischer Tr. 131:8-22; Davies Tr. 462:23-463:11.) Finally, Mr.

Fischer used dry mixing in his formulation of Zubsolv®. (Fischer Tr. 151:1-8, 223:12-19.) Dry mixing combines the particles together without fluid, and the particles adhere to each other by interactive forces. (*Id.* at 142:10-144:5, 151:1-8; JTX-0001.0018.) However, Mr. Fischer testified that the asserted patents teach that compositions of the invention may also be formulated by way of [redacted] so "the particles end up in the same way as when you did dry mixing." (Fisher Tr. 144:2-24; JTX-0001.0015.)

D. Sun's ANDA Products

Sun filed ANDA No. 214737 pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (the Federal Food, Drug and Cosmetic Act ("FFDCA")) with the FDA which sought approval to commercially market a generic version of Zubsolv® (buprenorphine/naloxone sublingual tablets at doses of 1.4/0.36 mg, 2.9/0.71 mg, 5.7/1.4 mg, 8.6/2.1 mg, and 11.4/2.9 mg) ("Sun's ANDA Products") before the expiration of the asserted patents. (ECF No. 341 ¶ 19.) In connection with Sun's ANDA and pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Sun filed written certifications which alleged that the asserted claims and asserted patents are invalid and unenforceable. (*Id.* at ¶ 20.) Additionally, Sun certified that Sun's ANDA Products do not infringe on the asserted patents. (*Id.*)

As part of seeking approval of its ANDA Products, Sun was required by the FDA to demonstrate that its ANDA Products were therapeutically equivalent or "bioequivalent" to Zubsolv®, *i.e.*, that they result in the same therapeutic response. (Davies Tr. 515:15-516:3.) To do so, Sun conducted a bioequivalence study [redacted] in the same dose strength of Zubsolv®. (*Id.* at 514:8-517:8, 518:15-18.) Sun's

data successfully demonstrated to the FDA that Sun's ANDA Products were bioequivalent to Orexo's Zubsolv® product. (*Id.* at 519:2-520:18; Singh Tr. 829:7-9.)

Sun uses [redacted]. (Davies Tr. 481:5-12.) The key dispute in this case is whether [redacted] or a composition in which the buprenorphine microparticles are separate from the weak acid particles, which is a key feature of the asserted patents and would therefore infringe.

E. The Patents-in-Suit

Orexo asserts that Sun's ANDA Products infringe on the '900 and '387 patents. (JTX-0003.0001, JTX-0005.0001.) The asserted patents are both titled, "Abuse-resistant pharmaceutical composition for the treatment of opioid dependence." (*Id.*) The asserted patents have substantially the same specification and claim priority to U.S. Provisional Application No. 61/536,180, which was filed September 19, 2011. (ECF No. 341 ¶ 22.) Accordingly, the priority date of the asserted patents is September 19, 2011, and are all assigned to Orexo AB. (*See generally* ECF No. 341.)

1. *The '900 Patent*

Orexo asserts claims 2 and 16 under the '900 patent, which are dependent on claim 1. Claim 1 of the '900 patent states:

> A pharmaceutical composition in the form of a tablet suitable for sublingual administration comprising:
>
> buprenorphine, or a pharmaceutically acceptable salt thereof, provided in the form of microparticles,
>
> a weak acid, provided in the form of particles, which particles are separate from the microparticles of buprenorphine, or a pharmaceutically acceptable salt thereof,
>
> a disintegrant,
>
> and naloxone or a pharmaceutically acceptable salt thereof,

wherein the per tablet dosage of buprenorphine (calculated as the free base) is 11.4 mg, 8.6 mg, 5.7 mg, 2.9 mg, or 1.4 mg;

and wherein the per tablet dosage ratio of buprenorphine: naloxone dose (calculated as free bases) is about 4:1.

[(JTX-0003.0026.)]

Claim 2 of the '900 patent states:

> The composition as claimed in claim **1** wherein the disintegrant is selected from the group of croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone and mixtures thereof.
>
> [(JTX-0003.0026.)]

Claim 16 of the '900 patent states:

> The composition as claimed in claim **1**, wherein the microparticles of buprenorphine or salt thereof are in associative admixture with the particles of weak acid.
>
> [(JTX-0003.0026.)]

2. *The '387 Patent*

Orexo also asserts claims 6 and 13 under the '387 patent. Claim 6 of the '387 patent, states:

> The composition as claimed in claim **1**, wherein the tablet has a hardness that is in the range of about 15N to about 50N.
>
> [(JTX-0005.0026.)[4]]

[4] Claim 6 of the '387 patent is dependent on claim 1 of the '387 patent. Claim 1 of the '387 patent states:

> A pharmaceutical composition in the form of a compressed tablet suitable for sublingual administration, which comprises:
>
> (i) buprenorphine or a pharmaceutically acceptable salt, particles comprising citric acid, thereof provided in the form of microparticles in a dosage amount (calculated as the free base) that is 11.4 mg (±12 %), 8.6 mg (±2 %), or 5.7 mg (±12 %);

Claim 13 of the ’387 patent states:

> The composition as claimed in claim **8**, wherein the tablet has a hardness that is in the range of about 15N to about 50N.
>
> [(JTX-0005.0026.)[5]]

The parties stipulated that all asserted claims require separate or distinct buprenorphine microparticles and weak acid particles. (ECF Nos. 338.)

> (ii) naloxone or a pharmaceutically-acceptable salt thereof provided in the form of particles in an amount (calculated as the free base) that is about ¼ of the above doses of buprenorphine or salt thereof;
> (iii) particles comprising a weak acid; and
> (iv) a disintegrant, wherein the tablet weighs no more than about 250 mg and has a hardness that is in the range of about 10N to about 100N, as measured by the US Pharmacopoeia method.
>
> [(JTX-0005.0026.)]

[5] Claim 13 of the ’387 patent is dependent on Claim 8 of the ’387 patent. Claim 8 of the ’387 patent states:

> (i) buprenorphine or a pharmaceutically acceptable salt thereof provided in the form of microparticles in a dosage amount (calculated as the free base) that is 2.9 mg (±2%);
> (ii) naloxone or a pharmaceutically acceptable salt thereof provided in the form of particles in a dosage amount (calculated as the free base) that is about ¼ of the above dose of buprenorphine or salt thereof;
> (iii) particles comprising a weak acid; and
> (iv) a disintegrant, wherein the tablet weighs no more than about 100 mg and has a hardness that is in the range of about 10N to about 100N, as measured by the US Pharmacopoeia method.
>
> [(JTX-0005.0026.)]

F. Procedural History[6]

Plaintiffs filed Civil Actions Nos. 20-12588 (consolidated), 21-13320, and 21-17941, which alleged various infringement claims against Defendants relating to the '198 patent, '330 patent, '361 patent, '421 patent, '900 patent, '661 patent, '010 patent, '387 patent, and '388 patent.[7] On March 18, 2022, the Court consolidated Civil Action Nos. 21-13320 and 21-17941 with this matter. (ECF No. 120.) The Court held a Markman Hearing on November 16, 2022. On January 25, 2023, the Court issued its claim construction decision. (ECF Nos. 340, 343.) The Court construed the term "weak acid" to be "an acid (proton donor) that only partly ionizes in water." (ECF No. 343 at 20.) The Court also defined a Person of Ordinary Skill in the Art ("POSA") as:

> A person who possesses a Ph.D. in pharmaceutical sciences or related fields with one to three (1-3) years of experience in the development of pharmaceutical formulations, or, in the alternative, a person who possesses a B.S. in pharmaceutical sciences or related fields, and at least five (5) years of experience in the development of pharmaceutical formulations.
>
> [(*Id*. at 9.)]

The Court entered the Final Pretrial Order on January 25, 2023. (ECF No. 341.) The Court held a one-week bench trial from January 30, 2023, to February 3, 2023. Orexo proceeded to trial with claims 2 and 16 under the '900 patent and claims 6 and 13 under the '387 patent. Sun counterclaimed seeking a declaratory judgment that Sun's ANDA Products do not infringe and that the asserted patents are invalid and unenforceable. (*See generally* ECF No. 19, Civ. No. 20-

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[6] This civil action arises under the United States patent laws, title 35 of the United States Code, so this Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

[7] Orexo asserted the '661 and '010 patents in Civ. No. 21-13320 (Compl. ECF No. 1, Civ. No. 21-13320), the '387 and '388 patents in Civ. No. 21-17941 (Compl. ECF No. 1, Civ. No. 21-17941), and the '198, '330, '361, '421, and '900 patents in Civ. No. 20-12588 (Compl., ECF No. 1, Civ. No. 20-12588.)

12588; ECF No. 7, Civ. No 21-17941.) The parties submitted their Proposed Findings of Fact on March 6 and 7, 2023 alongside their post-trial briefs. (*See* ECF Nos. 380-382.) The parties submitted their post-trial reply briefs on March 23, 2023. (ECF Nos. 387, 388.) Closing arguments were held on March 30, 2023.

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Infringement

Patent infringement occurs when a person "without authority makes, uses[,] or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). The patentee bears the burden of demonstrating infringement by a preponderance of the evidence.[8] *Eli Lilly & Co. v. Hospira, Inc.*, 933 F.3d 1320, 1328 (Fed. Cir. 2019) (citation omitted). A preponderance of evidence has been defined by the United States Court of Appeals for the Federal Circuit as "the greater weight of evidence, evidence which is more convincing than the evidence which is offered in opposition to it." *Hale v. Dep't of Transp., F.A.A.*, 772 F.2d 882, 885 (Fed. Cir. 1985); *In re Winship*, 397 U.S. 358, 371–72 (1970) (Harlan, J., concurring) (defining a preponderance of evidence as "the existence of a fact is more probable than its nonexistence[.]"). "To show infringement of a patent, a patentee must supply sufficient evidence to prove that the accused product or process contains . . . every limitation of the properly construed claim." *Seal-Flex, Inc. v. Athletic Track & Court Const.*, 172 F.3d 836, 842 (Fed. Cir. 1999). If any claim limitation is not present, then the challenged product does not infringe as a matter of law. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). "A patentee may prove infringement by any method of analysis that is probative of the fact of infringement," and

[8] Orexo, as the patentee of the asserted patents, bears the burden of proving by a preponderance of evidence that Sun infringed upon the asserted patents.

"circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (internal citations omitted).

The parties stipulated prior to trial that the only issue regarding infringement is whether Orexo has proven by a preponderance of the evidence that Sun's ANDA Products meet the claim limitation in all asserted claims requiring separate (*i.e.*, distinct) buprenorphine microparticles and particles comprising weak acid – the separateness limitation. (ECF No. 341 ¶ 63(1)b.) The parties also stipulated that if the Court finds for Orexo on the separateness issue, then Orexo will have met its burden of proving infringement for the asserted patent claims, subject to Sun's invalidity defenses. (*Id.* ¶ 63(1)c.)

At trial, Orexo presented evidence claiming that Sun used the asserted patents as a "roadmap" and that Sun's ingredients and manufacturing process results in separate particles of buprenorphine and weak acids thereby infringing on the asserted patents. In support of its theory, Orexo also presented evidence regarding the following four data sets to show that Sun's ANDA Products possess separate buprenorphine and weak acid particles and thus infringe Orexo's patents: (1) Raman/SEM data; (2) Sun's PK data; (3) Sun's dissolution data, and (4) pH drip data. In response, Sun presented evidence that [redacted], which results in composite particles that are not separate and discrete and therefore are non-infringing. The Court will address each of these in turn.

1. *Sun's ANDA Ingredients and Manufacturing Process*

First, the Court finds that Sun's ANDA Products contain the same active ingredients as Zubsolv® – buprenorphine and naloxone.[9] (PTX-0030.0002-0003, 0018.) Sun's ANDA Products

[9] Sun's corporate representative testified that it is an FDA requirement for Sun's ANDA Products to have the same active pharmaceutical ingredient and in the same amount as Zubsolv®. (Singh Tr. 819:13-22.)

also contain similar inactive ingredients as Zubsolv®, [redacted]. (Davies Tr. 469:25-470:5; PTX-0030.0003, 0004, 0018.) Just like Zubsolv®, Sun's ANDA Products also contain [redacted] (JTX-0001.0015.) Sun's ANDA Products also contain the same five dosage strengths and in the same dosage form as Orexo's product. (Davies Tr. 468:12-469:24, 470:6-18, 471:7-8; PTX-0030.0002-0003, 0018.)

[redacted]

Orexo claims that [redacted] yields separate buprenorphine and weak acid particles in its ANDA Products because [redacted] and instead it maintains its particulate nature as opposed to [redacted] Orexo claims that [redacted] and that the asserted claims are

[redacted]

[redacted]

composition and not process claims, so the final composition is what matters for purposes of infringement and "not what happens in the process by which it is made." (ECF No. 381 at 17.)

To prove infringement, Orexo called Dr. Martyn Christopher Davies, an expert in pharmaceutical sciences and physical analytical chemistry to opine on the issue of infringement. (Davies Tr. 452: 12-20, 488:16-18, 453:1-4.) Dr. Davies did a comparison of Sun's ANDA process disclosed in its Quality Overall Summary ("QOS") [redacted]. (*Id.* at 480:5-24.) Dr. Davies opined that Sun used the asserted patents as a "roadmap" in designing [redacted] for its ANDA Products. (*Id.* at 481:5-14.)

Dr. Davies further testified that [redacted] (*Id.* at 481:21-25, 482:1-13.) Dr. Davies also testified that Sun does not intend for [redacted]. (*Id.* at 485:25, 486:1-14.) Dr. Davies explained that it "would make no sense to [redacted]

[redacted]

[redacted] (*Id.* at 486:18-20.) Finally, Dr. Davies explained that Sun's QOS is "able to characterize [the buprenorphine] in crystal form and that it's a consistent crystal form" and that one would not "go to the trouble of characterizing your crystal form if your [redacted]" (*Id.* at 488:16-489:4.)

[redacted] that release protons and drop the pH thereby facilitating a more rapid buprenorphine dissolution. (*Id.* at 490:16-22, 491:20-23.) Dr. Davies testified that [redacted] do not form a composite because "there is nothing else for them to form a composite with" so "you end up with particles that are separate." (*Id.* at 491:5-6, 495:23-24.) Accordingly, Dr. Davies opined that "Sun's ingredients and Sun's manufacturing process support my opinion that Sun's ANDA products meet the separateness limitation of the asserted claims." (*Id.* at 497:2-4.)

In response, Sun presented testimony from Marcus Laird Forrest, Ph.D., an expert in the field of pharmaceutical sciences, including the formulation and manufacturing of tablet formulations. (Forrest Tr. 719:10-12.) Dr. Forrest opined that Sun's ANDA Products do not meet the separateness limitation because Sun's manufacturing process "simply won't result in separate microparticles at the end" because the [redacted] to "maintain the nature of the original starting material" as a "separate and distinct" particle so you end up with a composite particle. (*Id.* at 722:13-25, 864:24-25, 865:1-7, 869:14-16.)

Dr. Forrest explained that [redacted]

[redacted]

explained that the "closest analogy I can think is you take a [redacted]." (*Id.* at 853:20-23.) Dr. Forrest described his analogy as follows:

[redacted]

[(*Id.* at 856:14-857:1.)]

Dr. Forrest testified that [redacted] and "what you're left with is just a single composite mass." (*Id.* at 858:7-15.) Dr. Forrest explained that the [redacted]. (*Id.* at 863:8-17.)

Second, Dr. Forrest testified that Sun did not [redacted] to get separate particles. (*Id.* at 866:21-24.) Dr. Forrest testified that [redacted]

[redacted] Sun used is "very, very different from the processes in the patent. In the patent, for example, [redacted]." (*Id.* at 867:3-9.) Dr. Forrest explained that the asserted patents only provide for dry mixing that "maintains the particles as separate particles so that the "citric acid is still free and separate from the buprenorphine," as used in Example 1, 3 and 6 to 8 of the asserted patents. (*Id.* at 726:18-22, 727:1-11.) According to Dr. Forrest, the asserted patents recognize the advantages of a formulation with an associative admixture, where the particles remain separate as it gave "rise to a significantly improved bioavailability for buprenorphine when compared to the prior art" or commercially available formulations such as Suboxone®. (*Id.* at 729:18-25, 730:13.)

Finally, Dr. Forrest testified to statements made by Orexo to the European Patent Office ("EPO") [redacted]. Dr. Forrest testified that Orexo told the EPO that "*[u]nless specific steps* are taken, a [redacted] will not result in distinct, separate particles of ingredients." (*Id.* at 869:22-25, 870:1-8; DTX-0071 (emphasis added).) Dr. Forrest explained that a POSA would understand this statement to mean "if you don't maintain [the particles, as independent and distinct particles] through your manufacturing process, you won't have a relevant composition at the end." (Forrest Tr. 755:5-10.)

Romi Singh, Sun's Senior Vice President, Formulation Development and Clinical Development, also testified on behalf of Sun. Dr. Singh was involved in the development of Sun's ANDA Products. (Singh Tr. 779:4-6.) Dr. Singh testified that Sun's [redacted] results in composite particles in which "all the ingredients bond together" and "they do not have the distinct physical identity." (*Id.* at 802:5-6, 809:19-810:2-4.) Dr. Singh also testified that

[redacted] (*Id.* at 808:18-19.) On direct examination, Dr. Singh was asked the following:

[redacted]

> Q. During the research and development, did Sun study the content of the buprenorphine particle to see exactly how the ingredients were arranged inside?
>
> A. No we did not.
>
> [(*Id.* at 808:20-809:6.)]

However, on cross-examination, Dr. Singh testified that [redacted] (Singh Tr. 808:13-15, 828:9-12.) Specifically, Dr. Singh was asked:

[redacted]

> [(*Id.* at 828:6-12.)]

In response, Orexo contends that the statements to the EPO should not be given weight because the statements were made in the context of distinguishing Suboxone® tablets from Orexo's invention and that the statements explain why Suboxone® tablets do not have separate particles.[11] (Davies Tr. 494:5-22.) Dr. Davies was asked the following:

> Q. And why don't these EPO statements impact your opinion?
>
> A. Firstly, this was an action in the EPO related to patents that are not within this case, that are different patents. And I'm told that different rules apply for the EPO other than this U.S. patent.
>
> But the point of all of this -- and you see it in the paragraph above, the highlighted area, where they are talking about Suboxone manufacture. And the whole point of this is to say, is to distinguish the claimed invention -- namely, separate particles of buprenorphine microparticles and the weak acid particles -- from Suboxone because Suboxone dissolves up the buprenorphine and the weak acid first in the granulating fluid before they add it to the powder. One of the examples I showed for forming a composite mixture, they do that. So the buprenorphine and the weak acid are in the same particle. They are in a composite mixture. They are intermingled. And the whole point of this is to explain to the Patent Office that the claimed invention is different to Suboxone.
>
> [(*Id.*)]

Additionally, Orexo contends that Sun did in fact take a "specific step" in manufacturing its ANDA Products [redacted]. (Davies Tr. 494:23-496:20.) Dr. Davies asserted that a POSA would know that [redacted] would lead to separate particles as [redacted]. (*Id.* at 494:23-496:20, 598:4-601:8.) Dr. Davies testified as follows:

> Q. Does Sun employ a specific step [redacted] to ensure that there are separate particles?

[11] Based on a review of the record, Suboxone® contains buprenorphine and citric acid in the form of a composite mixture. (Fischer Tr. 149:9-150:9; Davies Tr. 467:16-468:11.)

A. Yes, it does, because Sun – I believe Sun does because Sun [redacted]

[(*Id.* at 495:1-7.)]

According to Dr. Davies and Dr. Singh, [redacted]. (*Id.*; Davies Tr. 490:6-22.) Simply put, Dr. Davies opined that Sun's [redacted] do not form composite particles with other ingredients because there is nothing for them to form a composite with because [redacted]. (Davies Tr. 490:6-491:8.) As a result, Orexo asserts that Sun's ANDA Products start with separate buprenorphine microparticles and weak acid particles and end with separate buprenorphine microparticles and weak acid particles.

Based on the Court's review of the evidence, there is no real dispute that [redacted]. (Davies Tr. 611:5-10; Davies Tr. 482:22-25; Forrest Tr. 942:10-943:6 (testifying that in Sun's ANDA Products [redacted])). When describing the general process Sun uses to make its ANDA Products, Dr. Forrest testified that the [redacted]. (Forrest Tr. 862:20-863:4.) When asked if there are "distinct particles of buprenorphine [redacted] Dr. Forrest responded as follows:

[redacted] I believe we heard earlier in the reports about sticking problems and issues with it being held together with other ingredients. And this goes into that [redacted]

[(*Id.* at 863:5-21.)]

On cross-examination, Dr. Forrest further testified:

[(*Id.* at 942:10-14).]

Based on Dr. Forrest's own testimony, Dr. Forrest admits that the

The Court does not find Dr. Forrest's jellybean theory convincing that the buprenorphine is no longer separate from the weak acid particles . Sun's process seems consistent with the specification. The patent provides that microparticles of buprenorphine and weak acid particles are presented in associative admixture. (JTX-0001.0015.) The patent refers to "associate admixture" as requiring "some form of mixing step (simple mixing, granulation as described hereinbefore, or otherwise)" as between buprenorphine microparticles and weak acid particles "rendering them in intimate contact with each other." (*Id.*) . (*Id.*) One could just as easily conclude that the causes the buprenorphine particles to be in "intimate contact" with the

weak acid particles. (Davies Tr. 557:7-11 (citing PTX-0096.0006 and stating that [redacted]); PTX-0096.0006 stating [redacted]).) Indeed, Dr. Forrest testified that [redacted] result in separate particles of buprenorphine and citric acid. (Forrest Tr. 939:18-22 (stating "I said that, yes, in theory it's possible. It would be quite an innovation, but in theory it is possible.").)

The Court does not find Orexo's statement to the EPO that "*[u]nless specific steps* are taken, a[redacted] will not result in distinct, separate particles of ingredients" dispositive of the issue. There is no evidence before the Court as to what specific steps Orexo was referring to when making that statement to the EPO. Indeed, Dr. Forrest testified that he did not see anything during the EPO proceedings or the U.S. prosecution where Orexo describes what specific steps would be needed [redacted] to make separate microparticles of buprenorphine. (Forrest Tr. 756:3-16.) And, Dr. Davies testified, Sun did in fact take a "specific step" in manufacturing its ANDA Products by [redacted]. (Davies Tr. 494:23-496:20.)

As a result, the Court finds Dr. Davies' testimony regarding Sun's manufacturing process and separateness to be more credible than Dr. Forrest's testimony. Accordingly, the Court finds that Orexo has proven by a preponderance of the evidence that Sun's [redacted] results in separate particles of buprenorphine and weak acid particles, particularly when viewed in conjunction with the additional evidence presented by Orexo. *See infra* Section II, B, 2,4.

2. *Dr. Bugay's Raman and SEM Testing*

Orexo presented testimony from David E Bugay, Ph.D., an expert in the field of analytical chemistry and particularly microscopy who conducted Raman[12] and Scanning Electron Microcopy ("SEM")[13] on Sun's ANDA Products. (Bugay Tr. 298:19-24.) Orexo contends that Dr. Bugay's data provides an independent basis for finding that Sun's ANDA Products meet the separateness limitation of the asserted claims.

Dr. Bugay testified that he used Raman and SEM on Sun's ANDA Products and buprenorphine granules. (*Id.* at 303:10-304:4, 304:23-25.) Dr. Bugay explained that his testing began by conducting a Raman spectra of Sun's thirteen individual ingredients, which acted as a control and a reference, or a chemical "fingerprint" of those components. (*Id.* at 307:18-21, 308:4-308:16.) Dr. Bugay explained that the Raman provides the "pattern or picture of peaks and valleys that are inherent to the chemical structure," which allows you to "differentiate one chemical

---

[12] According to Dr. Bugay, Raman microscopy "is a chemical identification technique. In other words, if you put three white powders in front of me, let's say, caffeine, sugar, and aspirin – acetylsalicylic acid – they are all three white powders, but by performing the Raman experiment on those three separate powders, I can actually chemically identify and tell you which one is caffeine, which one is sugar, and one is acetylsalicylic acid. So a chemical ID technique." (Bugay Tr. 300:24-301:6.)

[13] According to Dr. Bugay, SEM is "a microscopy technique in which an image is produced of the material of interest," but "your image is of much higher quality, higher resolution, meaning the distance from one sampling point to another is super small and you are able to get some three-dimensional aspect of your sample." (Bugay Tr. 302:8-17.) Dr. Bugay provided the following example:

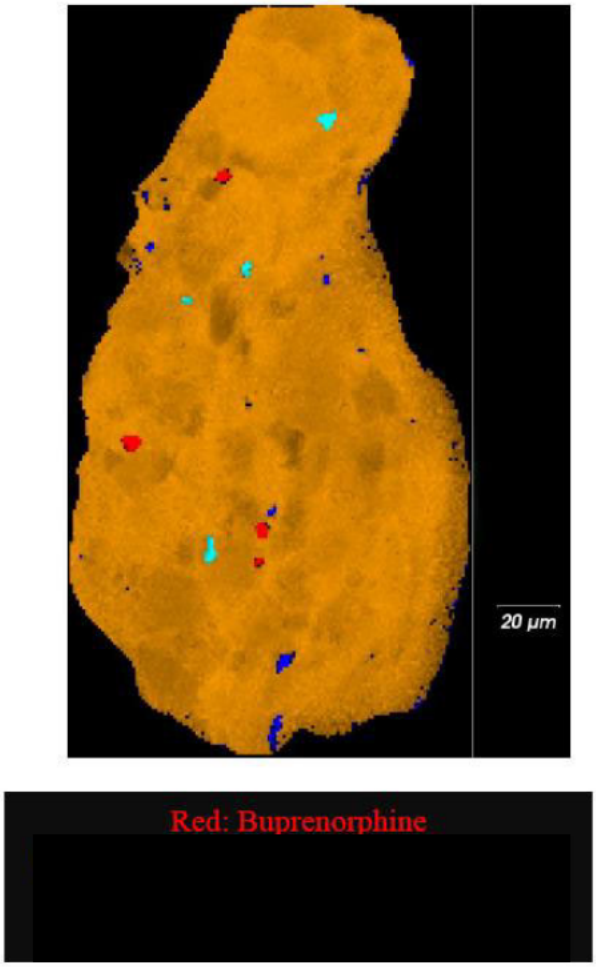
> [I]f I look at this piece of wood, for example, you know, from this vantage point, it looks smooth. If I use the electron microscope, I could actually see grain in the pores that exist in the wood. And so that's what I mean by higher resolution and that higher magnification of that particular technique."
>
> [(Bugay Tr. 302:19-24.)]

component from another." (*Id.* at 313:22-314:1-7.) This process acts as a control, where the "known spectrum . . . represents the individual components." (*Id.* at 315:1-4.)

Next, Dr. Bugay analyzed eight of Sun's individual buprenorphine granules by using Raman and SEM so he could have an understanding of the "preliminary material that is then subsequently incorporated into the tablet." (*Id.* at 308:17-23, 336:18-341:23; PTX:0289-0304; PTX:0195-0211.) Dr. Bugay's testing of the granules did not reveal [redacted] (Bugay Tr. 315:5-316:15.) Dr. Bugay generated Raman maps for the eight granules he analyzed. (*Id.* at 320:4-13.) An example of the Raman microscopy is as follows:

Raman Image of Sun Buprenorphine Granule

[redacted] Image No. RM4-894;
Sample No. 1241-8-3; Corresponds to SEM1-151-2)



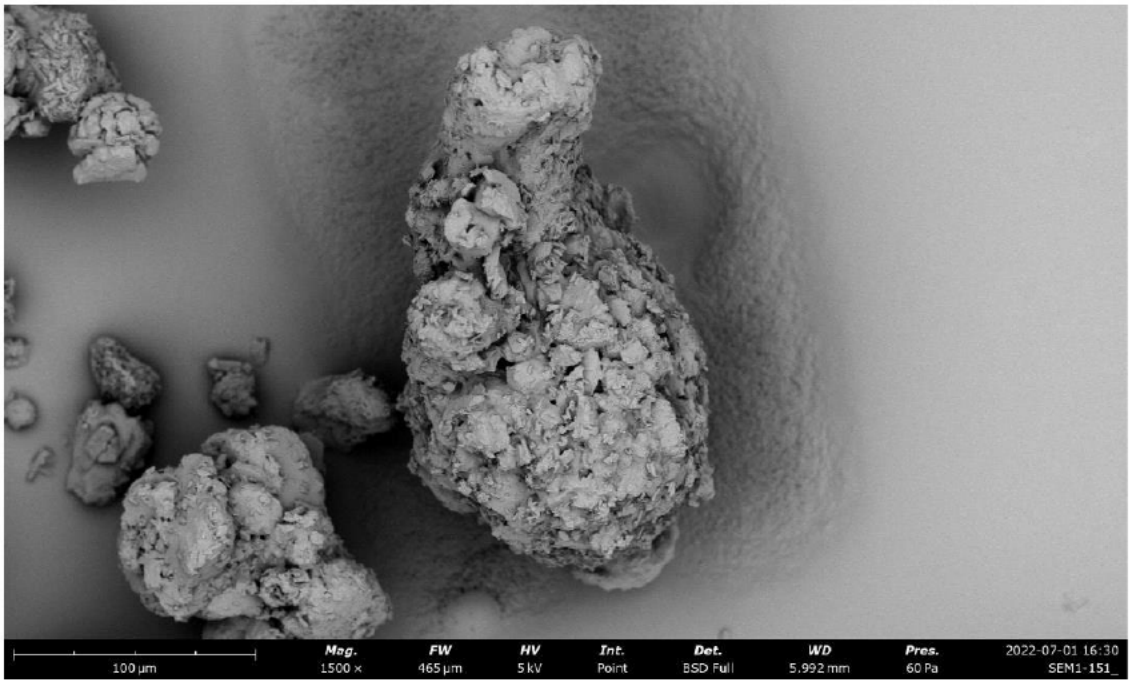
[(PTX-0300.)]

The Raman maps showed the "color coding for whether buprenorphine (color coded as red) or the [redacted] color coded as blue) was present or not" as well as the carrier particle (either in yellow or orange). (*Id.* at 320:8-13.) Again, Dr. Bugay explained that "Raman is a very specific and powerful technique to be able to measure whether there is a chemical composition of more than one component or whether you have a singular component." (*Id.* at 329:21-330:3.) Dr. Bugay testified that the "Raman spectra would not match to those reference or control samples" if you saw a composite mixture. (*Id.* at 330:4-7.)

With respect to Dr. Bugay's SEM of the buprenorphine granules, Dr. Bugay testified that the SEM allows him to "investigate the physical characteristics of the same eight granules," meaning "whether those domains of buprenorphine and [redacted] were actually particles or not." (*Id.* at 332:22-333:6.) Dr. Bugay explained that the SEM "allows one to determine if those distinct attributes of size, shape, face, angles, and such were present, allowing for determination of a particle or not." (*Id.* at 333:7-13.) Dr. Bugay testified that the buprenorphine previously identified by Raman could now be seen as an actual particle that has "an outline to it. It has a shape. It has some edges. It has a three-dimensionality that allows it to be characterized as a particle." (*Id.* at 337:2-10.) The same result was seen with respect to the [redacted] (*Id.*) An example of the SEM of the granules is as follows:

SEM Image of Sun's Buprenorphine Granules
[redacted]; Image No. SEM1-151_2;
Sample No. 1241-8-3; Corresponds to RM4-894)

PLAINTIFF'S EXHIBIT
PTX-205



[(PTX-0205.)]

Dr. Bugay did acknowledge that there were examples of buprenorphine and weak acids that were touching or in contact, but there was no "intermixing of the two" and they remained "separate particles" as identified by the Raman testing. (*Id.* at 339:18-340:19.) Dr. Bugay testified that the combined Raman and SEM testing of the granules showed that "[o]n the surface of [the] carrier particle, [redacted] there was separate and distinct particles of the buprenorphine separated from weak acid particles." (*Id.* at 312:20-25.)

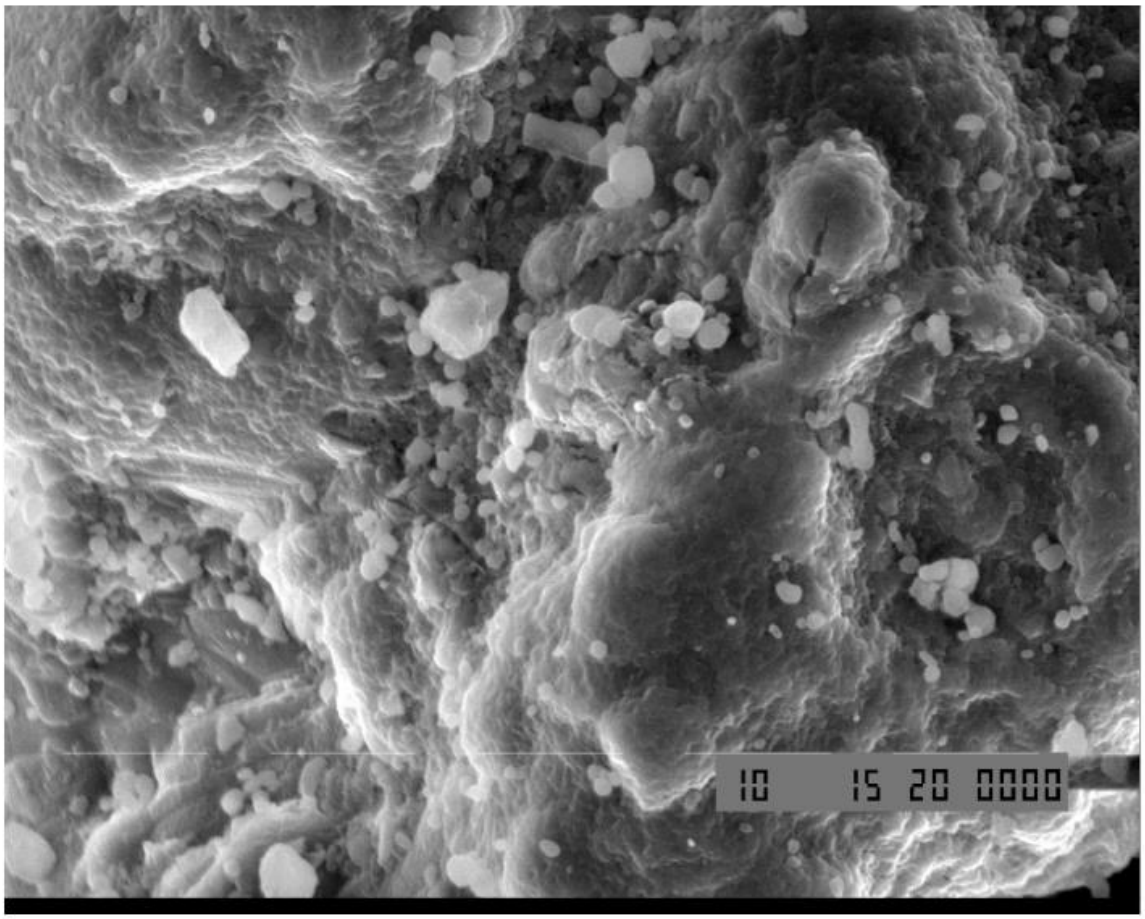
Finally, Dr. Bugay analyzed fifteen of Sun's tablets to determine "whether there was consistency in the buprenorphine microparticles with respect to being separate and distinct from the particles of weak acid." (*Id.* at 310:3-7, 344:8-9.) Dr. Bugay conducted a Raman chemical image for the tablets and found the arrangement of the ingredients in Sun's buprenorphine granules consistent with the arrangement of the particles in all fifteen of Sun's tablets. (*Id.* at 343:8-9, 344:6-11, 345:3-10.) Based on his testing, Dr. Bugay found that "[f]rom a combination of the Raman microscopy and [SEM], my investigation showed that Sun's ANDA products contain separate buprenorphine microparticles as well as weak acid particles and that the granules are not composite particles." (*Id.* at 311:16-20.) Dr. Bugay explained that "the consistency in the separate and distinct locations of the buprenorphine as compared to the weak acid particles . . . carried on from the granule to the tablets." (*Id.* at 312:9-12.)

Sun's expert, Dr. Forrest disagreed with Dr. Bugay's conclusion that Raman and SEM show separate and distinct particles of buprenorphine. (Forrest Tr. 900:8-10.) Dr. Forrest testified that the patent only discloses a pH drip test in the dissolution of the buprenorphine and not Raman and SEM and that the patent's reference to "microscopy" is for purposes of particle size and not determining separateness. (*Id.* at 900:11-901:13.) Dr. Forrest also testified that "while [he] agree[d] [Dr. Bugay's] testing was good[,]" Dr. Bugay's reading of the SEM was "too much and

ignore[es] that we have, you know, a single composite particle here, where there is other features that almost look to the human eye to be particles but we know they're part of the single composite." (*Id.* at 903:20-25.) Dr. Forrest testified that Raman and SEM do not show anything beneath the surface and so "it can't detect the composite, especially if that composite occurs under the surface because the Raman only sees the surface. It can't see where its glued and meld together in a full three – 360 degrees and underneath." (*Id.* at 904:17-21, 908:9-17.) Dr. Forrest testified that based on his review of Dr. Bugay's Raman and SEM images, he sees a composite particle based on his "years of experience looking." (*Id.* at 907:16-25.)

Finally, Dr. Forrest explained that Dr. Bugay failed to show a Suboxone® granule as a positive control of a composite particle. (*Id.*) Sun also relies on a 2013 presentation prepared by the inventor, Mr. Fischer which includes an SEM image of an interactive mixture of buprenorphine and mannitol carrier particles. (PTX-0471.0013, 0014.) Sun claims that Mr. Fischer's image, which shows separate buprenorphine microparticles, does not look like Dr. Bugay's images of Sun's buprenorphine granules. (PTX-0471.0014.) Mr. Fischer's image is as follows:

SEM image of an interactive mixture of buprenorphine HCl on mannitol



[(*Id.*)]

Mr. Fischer explained that the image was a "zoom[ed] in" version. (Fischer Tr. 219:23-220:7.) Sun argues that Mr. Fischer's images of separate and distinct buprenorphine "look nothing like Dr. Bugay's images of Sun's granules." (ECF No. 380 at 22.)

On cross examination, however, Dr. Forrest admitted that he had not cited any academic literature to support the opinion that Raman could not be used for a product [redacted] such as Sun's ANDA Products. (Forrest Tr. 916:1-14.) He also testified that he did

not run any Raman or SEM testing in this case, nor did he review the electronic Raman data that underlies Dr. Bugay's spectra as he did not have "the exact software package." (*Id.* at 917:10-24.) Finally, Dr. Forrest acknowledged that the patent does not need to disclose the type of testing that can be used to assess infringement. (*Id.* at 922:16-21.)

The Court finds Dr. Bugay's testimony credible for finding that Sun's ANDA Products meet the separateness limitation of the asserted claims. Sun attempted to rebut Dr. Bugay's testimony but was unsuccessful. First, Sun's own witness, Dr. Forrest agreed that the patent is not required to disclose all methods of testing for infringement. (Forrest Tr. 922:22-25; *see also* ECF No. 380 at 20 (stating "While testing for infringement does not necessarily need to be disclosed in a patent"); ECF No. 332 at 17 (stating "testing is neither needed nor appropriate to prove infringement.")); *see Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 667 (Fed. Cir. 1988) (affirming district court's finding of infringement even though the district court did not consider testing to determine the composition of the product). Further, the asserted patents disclose the use of microscopy and Dr. Forrest testified that in 2011 Raman and SEM were well-known techniques of microscopy. (JTX-0001.0014.) And, as Mr. Fischer testified, the patent refers to microscopy, which helps you "visualize the object you study" and there are different types including Raman and SEM. (Fischer Tr. 155:16-156:8.)

Second, Dr. Forrest testified that Raman testing would not be conclusive evidence for showing separateness on a product made [redacted]; however, Dr. Forrest admitted that he cited no literature to support his assertion. (Forrest Tr. 916:1-7.) Moreover, Sun agrees that "[s]canning electron microscopy in conjunction with Raman microscopy can be useful for examining particulate samples." (ECF No. 341 ¶ 65(4)(c).) Additionally, Dr. Forrest attempted to rebut Dr. Bugay's testimony by testifying that Raman and SEM cannot see below the surface of

the particle, but Dr. Forrest failed to provide any data or visuals to contradict this testimony other than to state he has spent "years of looking at it." (Forrest Tr. 904:22- 905:6, 907:16-25.) Indeed, Dr. Forrest admitted that he did not run any Raman or SEM testing in this case, nor did he review the electronic Raman data that underlies Dr. Bugay's spectra as he did not have "the exact software package" available to read the data. The Court finds Dr. Forrest's testimony in this regard not credible. (*Id.* at 917:22-24.)

Third, Dr. Forrest criticizes Dr. Bugay for failing to include a control in his testing. However, Dr. Bugay testified that his first step was to collect the Raman reference spectra on the control samples, and that the individual components of Sun's ANDA Products were a sufficient control and provided him a representative sample of their individual components. (Bugay Tr. 313:3-7.) Dr. Bugay explained that the reference spectra "act as a control. They act as a known response, known pattern . . . that represents the individual components." (*Id.* at 314:22-315:4.) As such, Dr. Forrest did not sufficiently show otherwise. As such, the Court will not give weight to Dr. Forrest's criticism regarding Dr. Bugay not using any controls. The Court further finds Dr. Bugay's testimony regarding his decision not to test Suboxone® as credible in that he did not "see the relevance. Those are different products made by a different process and so, therefore, don't act as a comparator. They don't act as a reference." (*Id.* at 364:25-365:7.)

Finally, Sun's reliance on Mr. Fischer's SEM image from 2013 to claim that the image is clearly different from Dr. Bugay's is unpersuasive as Sun fails to submit any testimony to substantiate or corroborate their argument.

For these reasons, the Court finds Dr. Bugay's Raman and SEM testing results credibly show that the buprenorphine microparticles are separate and distinct from the [redacted]

3. *Sun's PK and Dissolution Data*

In further support of its position that Sun's ANDA Products meet the separateness limitation, Orexo put forth evidence of Sun's PK data. PK refers to the measurement of blood levels of a drug at various timepoints, starting from the time it is first absorbed into the bloodstream and ending upon the drug's excretion from the bloodstream. (Davies Tr. 515:4-14.) The closely related concept of "bioavailability" refers to the measurement of how much of the drug ultimately ends up in the bloodstream. (*Id.* at 515:15-516:3.)[14] As part of seeking approval of its ANDA Products, Sun was required by the FDA to demonstrate that its ANDA Products were therapeutically equivalent or "bioequivalent" to Zubsolv®, *i.e.*, the two products are expected to give the same therapeutic response. (*Id.* at 514:15-515:3; Singh Tr. 821:17-20 (testifying that as a requirement from the FDA, Sun's ANDA Products have to be bioequivalent to Zubsolv®); 21 U.S.C. § 355(j)(2)(A)(iv) (stating an abbreviated application for a new drug shall contain information to show that the new drug is bioequivalent to the listed drug).)

After conducting its bioequivalence study, Sun reported its comparative data, including Cmax and AUC0-inf values, in the Clinical Summary Section of its ANDA. (PTX-0078.0078.) Sun reported comparative Cmax values of [redacted]. (*Id.*) Sun also reported comparative AUC0-inf values of [redacted]. (*Id.*) The parties do not dispute that [redacted] (Davies Tr. 519:2-520:18; Shahi Tr. 435:18-24.) Indeed, Sun's ANDA and the FDA's Tentative Approval letter confirm that Sun's ANDA Products

[14] Mr. Fischer likewise testified that pharmacokinetics looks at "how much of the active ingredient you have in the bloodstream at the particular point in time" and bioavailability also looks at "the amount of the active ingredient that has entered into the bloodstream." (Fischer Tr. 159:20-160:4.)

are bioequivalent and therapeutically equivalent to the reference listed drug, Zubsolv®. (DTX-0177.0017; PTX-0075.)

Dissolution testing is performed in the laboratory to determine the rate at which the drug is released from a dosage form. (Davies Tr. 525:3-5, 525:13-24.) As part of its ANDA submission, Sun provided dissolution studies comparing the rate at which buprenorphine is released from Sun's ANDA Products relative to Zubsolv®. (PTX-0078.0017-0061; DTX-0177.0036; Davies Tr. 524:17-24.) Sun's dissolution data [redacted]. (DTX-0177.0036; Davies Tr. 527:7-22.)

Orexo presented testimony from Dr. Davies that the [redacted] is indicative of the fact that both products have the same bioavailability and therefore Sun's ANDA Products have separate particles. (Davies Tr. 521:1-15.) Dr. Davies' opinion was based on the Patent Examiner's statement of reasons for allowance which indicated that the "tablet exhibits superior buprenorphine bioavailability" when the buprenorphine and weak acid are not in the same particle. (*Id.* at 523:11-20; JTX-0008.1410.) Dr. Davies likewise testified that the [redacted] indicate increased bioavailability consistent with separate buprenorphine microparticles and weak acid particles. (Davies Tr. 528:5-21.)

In response, Sun relies on Dr. Forrest's testimony that although Sun's ANDA Products are bioequivalent to Zubsolv®, it is "not uncommon" for two products to be bioequivalent even if their respective formulations and manufacturing process are different. (Forrest Tr. 868:7-25.) Dr. Forrest testified that "you can use very different manufacturing process and [redacted] which is not unusual in the formulation world." (*Id.* at 868:7-25.)

The Court finds that Sun's PK and dissolution data does not provide an independent basis for finding that Sun's ANDA Products meet the separateness limitation. "Bioequivalency is not the test for infringement." *Reckitt Benckiser LLC v. Aurobindo Pharma Ltd.*, 239 F. Supp. 3d 822, 833 (D. Del. 2017), *aff'd*, 737 F. App'x 537 (Fed. Cir. 2018) (citing *Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009)). "Bioequivalence is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes." *Reckitt*, 239 F. Supp. 3d at 833 (granting summary judgment for defendant after finding defendant's product did not infringe on plaintiff's patents because the asserted patents recited structural limitations on two distinct formulations, and plaintiff failed to identify how defendant's product contained these two distinct formulations aside from being bioequivalent).

Similar to the court in *Reckitt*, the Court here cannot conclude that the [redacted] alone proves separateness when Mr. Fischer and Dr. Davies both admit that a POSA could develop a non-infringing technique to produce the same dissolution and bioavailability results. (Fischer Tr. 193:20-23 (testifying that he could think of other techniques that might give the same rapid buprenorphine dissolution other than using separate buprenorphine and weak acid particles); Davies Tr. 571:2-14 (testifying that it is possible for a person of ordinary skill in the art to come up with a way to use a non-infringing technique to produce the same pH profile and dissolution results disclosed for the claimed invention).)

4. *pH Testing*

Orexo also argues that its pH drip data also provides an independent basis for finding that Sun's ANDA Products meet the separateness limitation of the asserted claims. The pH drip testing disclosed in the '330 patent is an *in vitro* test that is designed to mimic the sublingual environment, *i.e.*, the conditions under the tongue. (Fischer Tr. 162:8-15.) It was designed by Mr. Fischer as a

way to determine if you have separate particles of citric acid and buprenorphine. (*Id.* at197:9-13, 200:9-24.). The pH profile identifies how rapidly the buprenorphine is dissolved under the tongue – the lower the pH the higher dissolution of buprenorphine. (*Id.* at 168:3-10.)

Example 5 of the asserted patents, titled "Comparative In Vitro Small-Volume Funnel Dissolution Experiment 1"[15] discloses the following:

> Tablets form the three above-mentioned tablet batches, as well as Suboxone tablets (buprenorphine 8 mg/naloxone 2 mg; Reckitt Benckiser Healthcare Ltd, Hull, UK) were placed on top of a Porosity 1 20 mm diameter silica filter in a 55 mm (upper inner diameter) glass funnel.
>
> Potassium phosphate buffer with a pH of 6.8 (USP/NF), which mimics saliva, was allowed to drip through a soft PVC plastic tube with an inner diameter of 3 mm onto the tablets at a rate, set by a peristaltic pump (Flocon 1003), of 2 mL per minute. The distance between the end of the plastic tube and the silica filter in the funnel was set at approximately 7.5 cm, in order, along with the dripping rate, to correspond to a force similar to the pressure of the underside of the tongue. The small amounts of water involved endeavor to mimic the low amounts of water available in vivo under the human tongue.
>
> pH was measured over time using a Mettler Toledo InLab Expert Pro electrode (pH 0-14; 0-100°C.) attached to standard Mettler Toledo 340 pH meter positioned at the outlet of the glass funnel.
>
> [(JTX-0001.0023.)]

In Example 5, the pH was plotted over time for the following four tablet batches which are shown in Figure 5 (Zubsolv® (squares); non-micronised buprenorphine equivalents (crosses); equivalents without citric acid/sodium citrate (diamonds); and Suboxone® (triangles)).

[15] Sun's expert, Edmund J. Elder, Jr. testified that the term "comparative" in the title of Example 5 means that the test is evaluating "similarities and differences of the samples." (Elder Tr. 644:22-645:1.)

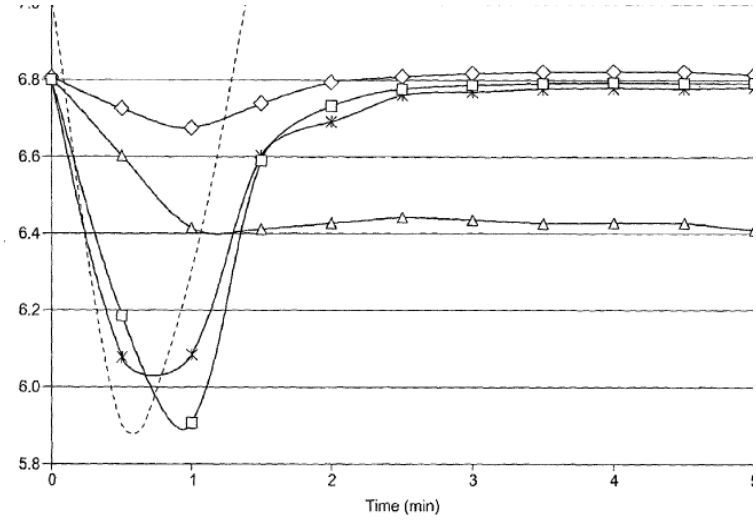


FIG. 5

[(JTX-0001.0023, JTX-0001.0008; Fischer Tr. 165:4-8.)]

Figure 5 shows that Zubsolv® displayed a rapid pH drop for about one minute, after which it returned to its original pH value whereas Suboxone® had a much slower decrease that stayed down for a longer time. (Fischer Tr. 164:19-165:18.) Figure 5 demonstrates that Suboxone® does not have a pH-timing effect because "you don't see a rapid, rapid drop in pH and then an increase back in pH," which is indicative of the buprenorphine and citric acid being in a composite mixture as opposed to separate particles of buprenorphine and citric acid. (Forrest Tr. 731:21-733:2; Fischer Tr. 199:24-200:15.)[16]

Orexo's witness, Matthew Greene ("Mr. Greene"), an expert in pharmaceutical formulations including pH analysis, provided testimony about pH testing he performed on Sun's ANDA tablets. (Greene Tr. 369:23-24, 374:4-5.) Mr. Greene tested nine tablets (three tablets from each of the three lots) that were provided by Sun at the same dosage strength–11.4 mg

[16] The citric acid causes the alternation in the pH. (Forrest Tr. 731:21-733:2 (testifying that "the citric acid is a separate particle that's free to interact with liquids and to dissolve very rapidly, that gives rise to this very rapid drop in pH," which is the pH-timing effect).)

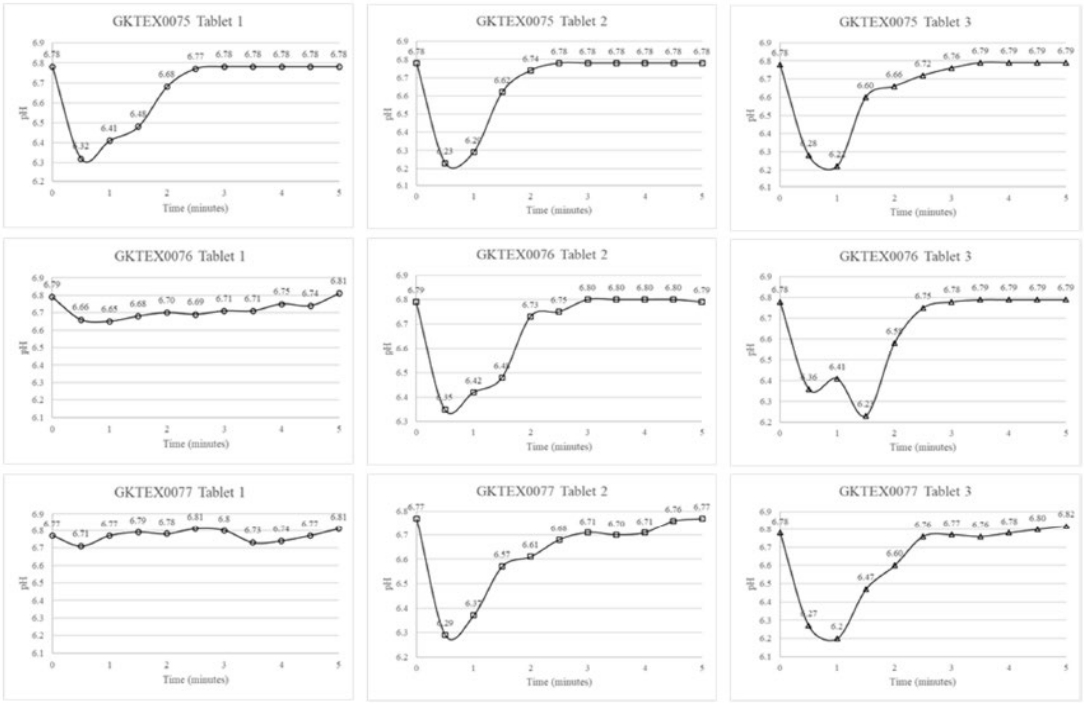
buprenorphine/2.9 mg naloxone. (*Id.* at 375:8-16, 388:12-20.) Mr. Greene did not conduct pH drip tests on tablets from Sun's other strengths.

Mr. Greene testified that he strictly followed the equipment setup and testing procedures disclosed in Example 5 of the asserted patents.[17] (*Id.* at 374:7-20, 376:19-23, 378:11-379:7; JTX-0001.) He further testified that he calibrated the pH meter using certified standards and calibrated the peristaltic pump that was used to a flow rate of 2mL per minute (as specified by the patent). (Greene Tr. 380:10-14.)

Mr. Greene's testing found that seven out of nine of Sun's tablets displayed a maximum drop of 0.4 to 0.6 pH units in about one minute and a return to the initial, native pH of the buffer in about three minutes, while two out of the nine tablets displayed no significant change in pH. (*Id.* at 374:7-20, 382:21-384:5.) Mr. Greene's results were as follows:

[17] Dr. Greene was originally provided the '421 patent, Example 5 for his testing, but for purposes of the trial referred to the '330 patent. (Greene Tr. 377:7-21.) There does not appear to be a dispute between the parties that the '421 patent is related to the asserted patents. (Elder Tr. 642:23-643:3 (Sun's expert testifying that he used the procedure outlined in the '421 patent for purposes of his pH drip testing and that his understanding is that the '421 patent is related to the asserted patents).)

Greene Plots – pH vs. Time Plots of Tablets from 3 Batches of Sun's ANDA Products



[(PTX-0509.)]

Mr. Greene did not conduct any testing on Suboxone® or Zubsolv® tablets. (*Id.* at 395:8-20, 396:16-22.)

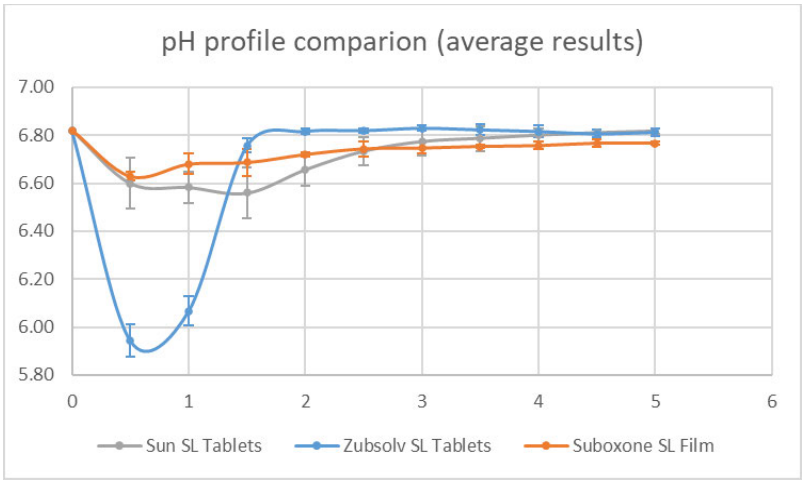
Sun presented testimony from its own expert in pharmaceutical formulation, development and analysis, Edmund J. Elder, Jr., Ph.D. ("Dr. Elder") who also conducted a pH drip test. (Elder Tr. 642:12-20.) Dr. Elder tested three tablets of Sun's ANDA product (one tablet from each of the three batches) at 5.7 mg of buprenorphine and 1.4 mg of naloxone, three Zubsolv® tablets at the same dose (three tablets from one batch) and three of the Suboxone® sublingual film (three samples from one lot) at the 8 mg of buprenorphine and 2 mg of naloxone as set forth in Example 9 of the patent.[18] (*Id.* at 647:14-648:10.) Dr. Elder testified that he included the Suboxone® film

[18] Example 9 of the patent, titled "Comparative In Vitro Small-Volume Funnel Dissolution Experiment II, seeks to obtain pH profiles for certain formulations as described in Example 8 as well as Suboxone® film (8 mg buprenorphine/2 mg naloxone) using the same dissolution procedure described in Example 5 of the patent. (JTX-0001.0024.)

as a negative control. (*Id.* at 659:10-14.) Dr. Elder explained that since "we are looking for definitive results, then we will include either a control or a comparator, which is a type of control. Or a reference standard, which is a type of comparator[.] This was a new method and not validated; so we needed to use controls[]" to ensure reliable results. (*Id.* at 660:6-13.) Dr. Elder testified that the Suboxone® film served as a negative control because there was no change in its pH. (*Id.* at 659:10-14.) Like Dr. Green, Dr. Elder also did not test Suboxone® tablets. (*Id.* at 676:6-7.)

Dr. Elder further testified that he followed the same procedure for conducting the pH drip test as outlined in Example 5 of the patent. (*Id.* at 642:21-25.) While Dr. Elder used a KD Scientific brand syringe pump instead of a peristaltic pump as indicated in the patent and he used a different brand of pH meter and electrode, these differences in equipment made no material difference in terms of the pH testing because of the ability to calibrate the instruments. (*Id.* at 649:23-650:12, 671:14-672-9.)

Based on his testing, Dr. Elder concluded that the Suboxone® film and Sun's tablets show no pH change as opposed to the Zubsolv® tablets that did show a pH change in his results. (*Id.* at 660:16-661:5.) Dr. Elder's results were shown in Figure 4 of his expert report as follows:



[(DTX-0519.0007, Fig. 4.)]

Dr. Elder then did an overlay of his results in Figure 4 with Figure 8 of the patent to demonstrate that his results were consistent with what was found in the patent. Figure 8 of Dr. Elder's report is as follows:

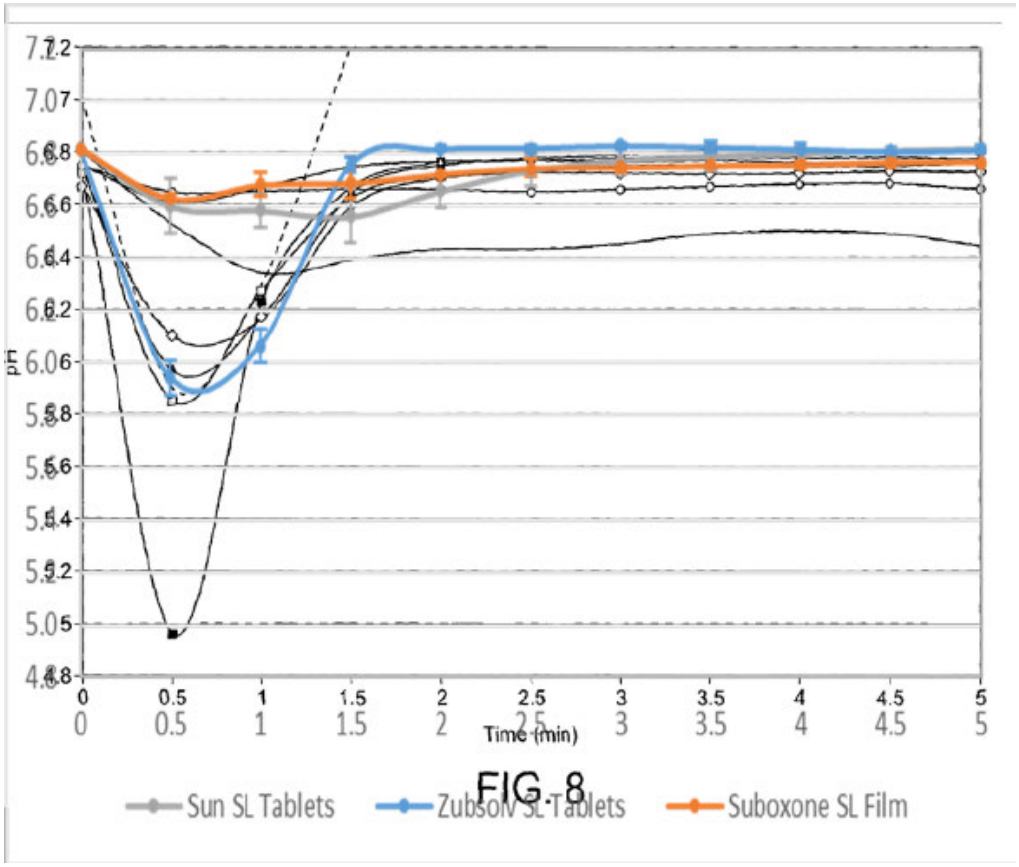


FIG. 8

[(DTX-0519.0011; Elder Tr. 660:19-661:12.)]

Dr. Elder testified that based on a standard statistical method, there was no statistically significant difference between the pH profiles of Sun's tablets and the Suboxone® sublingual film. (Elder Tr. 665:4-18.)

On cross-examination, Dr. Elder testified that he had never performed the pH drip test described in the patent before. (*Id.* at 668:1-2.) He also testified that calibrating the different equipment he used will give "reliable results," but he did not confirm that calibrating a pH meter will give "reproducible results." (*Id.* at 671:15-672:10.) Dr. Elder testified that "reproduction has

to do with the samples that you test." (*Id.* at 672:6-7.) He also confirmed that despite being provided all five strengths of Sun's ANDA products he did not test the 11.4 mg strength because he was not asked to. (*Id.* at 679:8-20.) He also was not aware that Sun used the 11.4 mg strength in its bioequivalence studies for the FDA and would not know the pH results for that strength without doing the tests. (*Id.* at 679:21-680-2.)

Orexo's expert, Dr. Davies testified that Mr. Greene's pH drip testing data "is another independent basis that supports [his] opinion that Sun's ANDA product meets the separateness limitation of the claims." (Davies Tr. 539:23-540:1.) Dr. Davies testified that Mr. Greene's pH drip testing results (PTX-0509) were consistent with Figure 5 from the asserted patents (JTX-0001.0008 at Fig. 5) and that Mr. Greene tested the highest dosage, which is representative of the lower dosage strengths. (Davies Tr. 529:16-530:19.) As for the two tablets that showed no pH drop, Dr. Davies explained that there could be "some issue with those tablets; potentially content uniformity issues." (*Id.* at 535:17-18.)

Dr. Davies also found Mr. Greene's testing [redacted] Zubsolv's® pH value of 5.5. (*Id.* at 531:4-532:17; PTX-0076.0004.) Dr. Davies testified that "Sun was measuring the pH because they wanted to match that of the Zubsolv, and what it tells you is both Sun's ANDA product and Zubsolv drop pH." (Davies Tr. 532:12-17.) Dr. Davies explained that a drop in pH is important because it improves the solubility of buprenorphine and allows it to get into solution quicker and absorbed quicker. (*Id.* at 532:18-24.) Dr. Davies testified that Sun's ANDA Products drop in pH because "they have the [redacted] in their product" as in Zubsolv®. (*Id.* at 532:22-533:7.) Dr. Davies testified that "the fact that Sun – pH drip profile

and [redacted] match that of the invention, match that of Zubsolv, is indicative of the fact that they have separate particles." (*Id.* at 533:23-534:5.)

With respect to the use of controls, Dr. Davies testified that the patent does not specify that controls are needed to be used or that statistics need to be performed, but rather the patent "asks you to follow a protocol." (*Id.* at 536:13-25.) Dr. Davies further explained that Figure 5 teaches a POSA that the pH drip test works and you do not need a control because "there is a sample which contains citric acid, so you could say that's a positive control. And there is a sample that doesn't contain citric acid, which is a negative control. If it doesn't contain a weak acid, you are not going get the drop in pH." (*Id.* at 537:16-20.) Dr. Davies explained that calibrating the pH probe will ensure that the test is working accurately. (*Id.* at 537:4-5.) Dr. Davies further testified that Suboxone® film is not a control, but rather part of a comparative study. (*Id.* at 538:7-14.)

As for Dr. Elder's pH testing, Dr. Davies testified that his data was [redacted]. (*Id.* at 538:16-22.) Dr. Davies explained that Dr. Elder's testing showing no drop in pH despite the fact that there is [redacted] is inconsistent "[redacted], but it's inconsistent with Mr. Greene's data." (*Id.* at 538:22-539:1.)

Sun's expert, Dr. Forrest testified that Dr. Elder's testing was reliable in that he incorporated controls, which confirmed that his testing was accurate. (Forrest Tr. 881:14-882:11.) Dr. Forrest explained that Zubsolv® was a positive control that showed a deep drop in pH as opposed to Suboxone® film, which was a negative control with no drop in pH. (*Id.* at 883:11-15.) Dr. Forrest explained that the use of a control "is an extra step beyond just calibration." (*Id.* at 886:3-6.) Dr. Forrest testified that controls are necessary and cited to a document from the FDA's Office of Regulatory Affairs that identifies general principles for quantitative and qualitative chemistry methods, which Dr. Forrest testified would include pH drip tests. (*Id.* at 886:25-887:22;

DTX-0082.) With respect to qualitative chemistry methods, the document provides for the analysis of a "quality control sample or reference material, if available." (DTX-0082.0008.)

Dr. Forrest also testified that Dr. Elder's testing was reliable because he also included a statistical analysis that removed any error caused by the human eye. (Forrest Tr. 881:14-882:11.) Dr. Forrest explained that Dr. Elder's results of the pH profile for Zubsolv® and Suboxone® film were consistent with the findings in Figure 8 of the patent. (*Id.* at 882:22-883:24.) Dr. Forrest testified that Sun's tablets look most similar to Suboxone® film and there was no statistical difference between the two. (*Id.* at 883:25-885:1.) Dr. Forrest concluded that there was no evidence of separateness as there was no pH drop. (*Id.* at 885:2-7.) Dr. Forrest testified that Sun's pH data was a "single static test" and not a pH drip test and that it was done to ensure the drugs stability and was not related to dissolution. (Forrest Tr. 880:9-881:5.)

Dr. Forrest was critical of Mr. Greene's pH testing in that Mr. Greene failed to use a control and he did not perform any statistical analysis to account for any variations in his testing. (*Id.* at 888:17-889:6.) Dr. Forrest also testified that there was "quite a bit of variation" in Mr. Greene's data. (*Id.* at 889:9-10.) Dr. Forrest explained that some samples that were tested showed no change in pH and in others there was a change in pH, but not at the level of a pH drop effect as discussed in the patent. (*Id.* at 889:21-890:1.) Although, Dr. Forrest admitted that seven of the nine tablets tested by Mr. Greene exhibited a pH drop of 0.4 or more. (*Id.* at 927:22-24.)

The Court finds Mr. Greene's pH testing of Sun's ANDA Products indicative of separateness as testified to by Dr. Davies. Mr. Greene's testing found that seven (7) out of nine (9) of Sun's tablets displayed a maximum drop of 0.4 to 0.6 pH units in about one minute and a return to the initial, native pH of the buffer in about three minutes (Greene Tr. 374:7-20, 382:21-384:5.), which was consistent with Figure 5 from the asserted patents. (JTX-0001.0008 at Fig. 5).

(Davies Tr. 529:16-530:19.) The matching pH drip profile of Sun's ANDA Products and Zubsolv® is a strong indication that Sun's ANDA Products have separate buprenorphine microparticles and weak acid particles. (Davies Tr. 533:23-534:5.)

Dr. Forrest testified that Mr. Greene's data had "quite a bit of variation" because some samples showed no change in pH and "in others, we see what appears to be a change in pH, although they didn't reach a threshold[] that the patent discussed as being reasonable thresholds of a pH drop effect."[19] (Forrest Tr. 889:7-890:5.) However, even if Sun is correct in their argument that four (4) out of the nine (9) tablets tested by Mr. Greene do not show a pH timing effect, the Court is persuaded that Orexo's showing five of (5) out of nine (9) tablets indicated a pH timing effect is probative of a finding of infringement.[20] *See Horizon Medicines LLC v. Alkem Lab'ys Ltd.*, 503 F. Supp. 3d 118, 155 (D. Del. 2020), *aff'd*, Civ No. 2021-1480, 2021 WL 5315424 (Fed. Cir. Nov. 16, 2021) (finding that the defendant's argument that because a majority – twenty-seven out of thirty-six – of the tablets did not meet the limitation, the plaintiff has not met its burden to prove infringement of that limitation unpersuasive); *see also Kaneka Corp. v. SKC Kolon PI, Inc.*, 198 F. Supp. 3d 1089, 1119 (C.D. Cal. 2016) (citing *Grain Processing Corp. v. American Maize–Products, Co.*, 840 F.2d 902, 911 (Fed. Cir. 1988) (stating "[a] patentee can prove infringement by showing that just 'some samples' or even 'a sample' of the product is found to meet all the limitations of a patent's claims.").

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[19] The asserted patents state, "[a]ccording to a further aspect of the invention, there is provided a pharmaceutical composition comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof, and particles of a weak acid or weakly acidic buffer forming materials, characterized in that the composition exhibits, in an in vitro small-volume funnel dissolution method, for example as described in Example 5 hereinafter: a) a pH drop of about 0.5 to about 5 pH units[.]" (JTX-0001.0020.)

[20] Mr. Greene agreed that two of the tablets did not exhibit a pH drop of 0.5 or greater. (Greene Tr. 394:13-25.)

Further, the Court does not find Mr. Greene's pH drip testing was unreliable for failure to test other formulations or conduct a statistical analysis as a control as claimed by Dr. Forrest. The protocol for the pH drip test is described in Example 5 of the asserted patents and does not describe or identify that other formulations be tested, or a statistical analysis be performed as a control to ensure the accuracy of the pH test. (Davies Tr. 536:13-537:3.) Rather, a reading of the patent indicates that the other formulations were tested, including some serving as controls (such as Suboxone® tablets or a sample containing citric acid) in order to provide a comparison of the various formulations and to analyze the pH drop. (Davies Tr. 537:10-538-6; Fischer Tr. 198:9-11.)

There is no dispute that Mr. Greene strictly followed the pH protocol set forth in the asserted patents by way of the procedure and equipment used.[21] (Greene Tr. 374:13-15.) The Court finds that calibration of the pH equipment was a sufficient control to ensure that his testing was accurate. (Davies Tr. 537: 6-9; Greene Tr. 380:10-14 (testifying that he "calibrated the pH meter using qualified, certified pH standards, and [he] calibrated the peristaltic pump to a flow rate of 2 mL per minute."); Elder Tr. 672: 16-20 (testifying that "[a] reference standard is a traceable reference" or "traceable standard for calibrating the pH meter.").)

The Court is unwilling to rely on Dr. Elder's pH testing. Contrary to Mr. Greene's testing of three tablets from each batch of Sun's ANDA Products, Dr. Elder only tested one tablet from each batch despite Dr. Elder acknowledging that "triplicate testing is a standard practice or a minimum number of samples that need to be tested in order to do any type of statistical analysis

[21] The only issue Sun raised in this regard is that Mr. Greene did not prepare a written protocol of his procedures before conducting his pH drip test. (Greene Tr. 386:10-14.) The Court does not find this to be a basis to challenge the reliability of Mr. Greene's testing as Mr. Greene testified that a written protocol was not necessary as the "written protocol was that of the patent." (*Id.*)

of the data and to show replication of results."[22] (Greene Tr. 375:13-376:1; Elder Tr. 647:22-24, 648:16-21.) Dr. Elder acknowledged that he tested the Zubsolv® tablets and Suboxone® film in "triplicate," but not Sun's ANDA Products. (Elder Tr. 647:14-648:15.) Further, Dr. Elder claimed that the results he obtained for Sun's tablets were "consistent" across the different batches because he calculated the standard deviation; however, Dr. Elder could not perform an analysis within each batch with having tested only one sample. (*Id.* at 654:4-11; DTX-0519.0004.)[23]

Further, Dr. Elder's testing was from Sun's 5.7 mg buprenorphine/1.4 mg naloxone sublingual tablets as opposed to the 11.4/2.9 mg strength, which is indicative of the other strengths. (Davies Tr. 530:16-19; Shahi Tr. 430:1-5.) Dr. Elder did not test the 11.4/2.9 mg strength despite it being provided to him, solely because he was not asked to. (Elder Tr. 679:8-20.) He also was not aware that Sun used the 11.4 mg strength in its bioequivalence studies for the FDA and wouldn't know the pH results for that strength without doing the tests. (*Id.* at 679:21-680-2.)

For these reasons, the Court finds that Orexo's pH evidence supports a finding that Sun's ANDA Products contained separate particles of buprenorphine and weak acid, which also supports a finding that Sun's ANDA Products infringed on the asserted patents.

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[22] Orexo claims Dr. Elder's results are not reliable because he deviated from the Example 5 procedure; however, Dr. Davies did not identify any criticism of how Dr. Elder conducted his pH drip test. (Davies Tr. 582:13-15.)

[23] Orexo also argues that Dr. Elder's results are not reliable because they are [redacted] The testimony, however, is clear that Sun's internal pH data was not generated as a result of a pH drip test as disclosed in the asserted patents but was rather for stability or bioequivalence purposes. (Davies Tr. 566:20-23; Davies Tr. 1175:3-16; Forrest Tr. 880:9-881:5; Singh Tr. 795:11-16.) Therefore, the Court will not compare it to Dr. Elder's pH test results.

5. *Infringement Conclusion*

As discussed above, Orexo, as the patentee, may prove infringement by any probative evidentiary method, which includes circumstantial evidence. *Martek*, 579 F.3d at 1372 (citation omitted). Based on the Court's review of the evidence, the Court finds that Orexo has met its burden of proving by a preponderance of the evidence that Sun's ANDA Products infringe upon the asserted patents, especially when evaluated in light of Sun's ANDA Products' manufacturing process and ingredients, Orexo's Raman and SEM microscopy, and Orexo's pH testing. *Lilly*, 933 F.3d at 1328 (noting that a patentee must prove infringement by a preponderance of the evidence). Following this, the Court finds that Sun's ANDA Products contain sperate microparticles of buprenorphine and weak acid particles. Therefore, the Court finds that Sun's ANDA infringes on claims 2 and 16 of the '900 patent and on claims 6 and 13 of the '387 patent.

B. Invalidity

A patent shall be presumed valid. 35 U.S.C. § 282(a). "The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." *Id.* A party may rebut the presumption of validity with clear and convincing evidence of invalidity. *Sciele Pharma Inc. v. Lupin Ltd*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (citing 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011)).

A high burden of proof is created by the necessary deference to the Patent and Trade Office (PTO). *Id.* This notion stems from the fact that the party challenging a patent in court "bears the added burden of overcoming the deference that is due to a qualified government agency presumed to have done its job. *Id.* (citing *PharmaStem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1366 (Fed. Cir. 2007)). That high burden is reflected in the clear and convincing evidence burden for proving invalidity. *Id.*

At trial, Sun asserted four reasons why the asserted patents are invalid and unenforceable: indefiniteness, written description, enablement, and obviousness. The Court will evaluate each of these arguments in turn.

1. *Indefiniteness*

A patent's "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor . . . regards as the invention." 35 U.S.C. § 112(b). Therefore, a patent is invalid for indefiniteness when its "claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). As the Supreme Court explained in *Nautilus*, language has "inherent limitations." *Niazi Licensing Corp. v. St. Jude Med. S.C., Inc.*, 30 F.4th 1339, 1346 (Fed. Cir. 2022) (citing *Nautilus*, 572 U.S. at 909). "The reasonable certainty standard exists to strike a 'delicate balance,' 'afford[ing] clear notice of what is claimed' while recognizing such inherent limitations." *Id.* (citation omitted). "This serves an important policy goal – providing clarity such that a person of ordinary skill in the art could determine whether or not an accused product or method infringes the claim." *Id.* at 1346-47.

The United States Court of Appeals for the Federal Circuit has previously found claims "indefinite where the claim requires a specific measurement or calculation, more than one measurement method may be used[,] and no guidance has been provided." *Pac. Coast Bldg. Prod., Inc. v. CertainTeed Gypsum, Inc.*, 816 F. App'x 454, 458 (Fed. Cir. 2020); *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1344-45 (Fed. Cir. 2015) (finding the claims to be indefinite because "average molecular weight" could be ascertained several different ways, and the claims did not indicate which measure to use); *Dow Chem. Co. v. Nova Chems. Corp.*, 803

F.3d 620, 635 (Fed. Cir. 2015) (finding the claim indefinite because the founder's chosen method was not an established method). Contrarily, the Federal Circuit has "refused to require that a patent disclose details as to every possible variable that may affect the calculation of a measured value or range of values recited in a patent claim." *Id.* Additionally, "a patent need not explicitly include information that is already well known in the art." *Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 875 F.3d 1369, 1376 (Fed. Cir. 2017). Instead, "[i]f a general approach is sufficiently well established in the art and referenced in the patent, then the claim is not indefinite." *Giesecke & Devrient GmbH v. United States*, 163 Fed. Cl. 430, 444 (2023) (citing *Presidio*, 875 F.3d at 1377).

Sun contends that the asserted claims are indefinite because different types of testing can yield different results, which prevents a POSA from knowing "the boundaries of the claim if different tests can be used to show infringement." (Forrest Tr. 975:6-9.) Specifically, Sun asserts that while the asserted patents disclose a pH drip test, they do not disclose Raman/SEM testing and those different tests can give different results as demonstrated by Dr. Elder's pH drip testing. (*Id.* at 973:21-975:9.)

Orexo argues that Sun's indefiniteness argument fails for two reasons: the parties agree on the meaning of the term "separate" as "distinct," and Sun's argument is contrary to the evidence. (ECF No. 381 at 44; ECF No. 50 at 2-3.)[24] Orexo contends that Dr. Bugay's Raman/SEM testing, Sun's PK data, Sun's dissolution data, and Mr. Greene's pH drip data ***all*** point to the same conclusion: that Sun's ANDA Products meet the separateness limitation. (ECF No. 381 at 44-45.) Dr. Davies testified that separateness could be proven by any of the testing methods discussed in

[24] Prior to trial, the parties agreed that the term "separate" means "distinct." (ECF No. 50 at 2-33; *see also* Forrest Tr. 1001:10-17 (testifying that "separate" and "distinct" mean the same).)

the specification, including pH drip testing, dissolution testing, PK testing and microscopy, and all that data has been consistent with each other in this case. (Davies Tr. 1167: 15-19; 1170:9-25.) However, Dr. Davies acknowledged that you do not need all tests to prove separateness, and that if dissolution and pH profile is inconclusive, a POSA would still have numerous sources of evidence to evaluate infringement. (*Id.* at 1169:8-1170:1.) Further, Orexo submits that the asserted patents disclose the use of microscopy to study the size of particles and that a POSA would understand that Raman and SEM can be used to assess the separateness of particles. (Fischer Tr. 155:16-156:8; Davies Tr. 511:18-512:2; JTX-0001.0014)

The Court does not find that the asserted patents are invalid based on indefiniteness as argued by Sun. As discussed above, the Court finds that Dr. Bugay's and Mr. Greene's testing are consistent with one another. Sun's argument that inconsistencies are evident because of Dr. Elder's testing is unpersuasive as the Court previously found Dr. Elder's testing unreliable due to the limited number of Sun's ANDA Products that were tested to be deemed a representative sample. Again, Dr. Elder only tested one tablet each from three batches of Sun's 5.7/1.4 mg ANDA Products. (Elder Tr. 647:14-18, 648:6-8, 648:12-15, 679:8-11.) As such, the Court does not find the asserted claims to be indefinite as Sun fails to show how different tests lead to different infringement conclusions; contrarily, the Court finds that the different tests support the same infringement conclusion. *See Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1366–67 (Fed. Cir. 2014) (stating "we do not believe that the mere possibility of different results from different measurement techniques renders [the claim] indefinite. Rather, the evidence established that *both* methods of measurement accurately report average particle diameter[.]").

Sun also argues that the specification does not provide guidance on how to use testing, like microscopy, to determine whether their ANDA Products contain separate buprenorphine and weak

acid particles. (ECF No. 380 at 29.) In support of its argument, Sun cites to *Pacific Coast Building Products*, *Teva*, and *Dow* for the proposition that a claim is indefinite "where the claim requires a specific measurement or calculation, more than one method may be used[,] and no guidance has been provided." *Pac. Coast Bldg. Prods*, 816 F. App'x at 458; *Teva*, 789 F.3d at 1344-45; *Dow*, 803 F.3d at 635. However, this case is different from those cases cited by Sun because the specification does in fact provide guidance to a POSA on how to determine separateness. (JTX-0001.0019 ("it is understood that the compositions of the invention give rise to such surprisingly increased bioavailability when compared to prior art . . . because of a pH-timing effect"); JTX-0001.0023 at Example 5.) Here, there is no dispute that the specification discloses a pH drip test and that a pH drip test can be used to show separateness. (Forrest Tr. 730:14-19; Fischer Tr. 162:2-168:10.) Further, there is no dispute that the patent need not disclose all the testing that can be used to assess infringement. (Forrest Tr. 922:16-25.)

For these reasons, Sun fails to prove by clear and convincing evidence that the asserted claims are indefinite.

2. *Written Description*

Pursuant to 35 U.S.C. § 112 ¶ (a), a patent's specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (internal brackets and quotation marks omitted). "The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the [invention] as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000).

"[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351. Disclosure is the "hallmark" of a written description, so possession is typically shown through disclosure. *See* i*d.* (stating '"possession as shown in the disclosure' is a more complete formulation."); *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1017 (Fed. Cir. 2022) ("the hallmark of written description is disclosure."); *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997) ("It is the disclosures of the applications that count."). This test requires the Court to perform an objective inquiry "into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

The Federal Circuit has made clear that a written description does not need to include examples "or an actual reduction to practice." *Ariad*, 598 F.3d at 1352. With respect to composition or product claims, the written description requirement does not demand that all methods of making the product be described in the specification. *AstraZeneca LP v. Breath Ltd.*, Civ. No. 08-1512, 2014 WL 2526909, at *5 (D.N.J. June 4, 2014); *Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1335 (Fed. Cir. 2003) ("the law makes clear that the specification need teach only one mode of making and using a claimed composition") (citation omitted); *Baldwin Graphic Systems, Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1344 (Fed. Cir. 2008) ("[c]ourts must generally take care to avoid reading process limitations into an apparatus claim . . . because the process by which a product is made is irrelevant to the question of whether that product infringes a pure apparatus claim."). Finally, whether a specification satisfies the written description requirement is a question of fact. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 729 (Fed. Cir. 2014); *see also Carnegie Mellon Univ. v. Hoffmann-La Roche*

Inc., 541 F.3d 1115, 1122 (Fed. Cir. 2008) ("Whether the written description requirement is satisfied is a fact-based inquiry that will depend on the nature of the claimed invention"). The party challenging the adequacy of a written description must do so through clear and convincing evidence. *Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005).

Sun argues that the asserted claims are invalid for lack of written description because a POSA would not recognize that the inventor possessed improved buprenorphine/naloxone formulations made [redacted]. (ECF No. 380 at 32.) Sun claims that the invention teaches only on way to achieve the claimed separateness, which is by dry mixing and the specification does not disclose a [redacted] (*Id.* at 33; Forrest Tr. 976:1-6.) Sun submits that the patent's [redacted] as further disclosed in column 8 and [redacted] JTX-0001.0015-0016; Forrest Tr. 981:9-984:15.) Sun maintains that Orexo used "word for word" the language in ([redacted]. (Forrest Tr. 984:11-985:9.) Moreover, Sun highlights that the inventor, Mr. Fischer considered [redacted], but ultimately rejected that approach and none of the

[redacted]

[redacted]

[redacted]

[redacted]

Examples in the patent disclose any testing showing that tablets made [redacted] have improved bioavailability. (*Id.* at 214:18-21, 979:4-980:1.) Accordingly, Sun contends that the inventor did not possess or understand whether [redacted] could result in tablets comprising separate buprenorphine and weak-acid particles, much less achieve improvements over Suboxone®. (ECF No. 380 at 36.)

In response, Orexo argues that Sun's arguments lack any legal merit as the asserted claims are composition claims and not process or method claims. (ECF No. 381 at 49.) Orexo submits that as a matter of law Sun has no basis to argue that the specification must disclose formulations made [redacted] to meet the written description requirement. (*Id.* (citing *AstraZeneca*, 2014 WL 2526909).) Moreover, Orexo argues that even if Sun had a legal basis to make such an argument, the specification is [redacted] (*Id.* at 45 (citing Davies Tr. 1161:14-1162:5, 465:15-466:14; Forrest Tr. 1002:15-1003:25.)

First, the Court finds that the asserted claims are composition/product claims. At trial, Sun's expert, Dr. Forrest agreed that the asserted claims were composition claims and not process claims. (*See* Forrest Tr. 956:14-21 (testifying that the asserted claims are not process claims); Davies Tr. 460:12-24 (testifying that what matters is whether the composition meets the limitation of the claim and not the process by which the composition is made).) Accordingly, the written description requirement does not demand that all methods of making the product, including those followed by Sun, be described in the specification. *Amgen Inc.*, 314 F.3d 1313, 131-32 ("When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise after the patent application is filed."); *AstraZeneca*, 2014 WL

2526909 at *5 (holding that the patent cannot be invalidated for failure to describe a method that is not itself claimed). Therefore, the asserted patents cannot be invalidated for failure to describe [redacted] as Orexo did not limit the claimed invention to a method of producing the claimed compositions. (Forrest Tr. 955:24-956:9 (testifying that the asserted claims do not contain a [redacted] limitation).)

Second, the Court finds that the inventor demonstrated to a POSA that he had, in fact, obtained a sublingual tablet comprised of separate microparticles of buprenorphine and weak acid particles. (*See, e.g.*, JTX-0003.0026 (describing the '900 patent in part as "the invention claimed is: [a] pharmaceutical composition in the form of a tablet suitable for sublingual administration comprising: buprenorphine, or a pharmaceutically acceptable salt thereof, provided in the form of microparticles, a weak acid, provided in the form of particles, which particles are separate from the microparticles of buprenorphine, or a pharmaceutically acceptable salt thereof.").) The patent explains how to make the claimed product in columns 3-11 of the specification and the specification makes clear that the compositions of the invention give rise to increased bioavailability, which is demonstrated by a pH-timing effect. (JTX-0001.0014-0019.) The specification provides the protocol for conducting the pH drip test and Figure 5 demonstrates the pH-timing effect for Zubsolv® over the prior art. (JTX-0001.0008, Fig. 5.) Moreover, column 6 provides that compositions of the invention may be formulated together by standard mixing techniques [redacted]. (JTX-0001.0015.) Indeed, Mr. Fischer testified that he considered [redacted]; however, he focused on and preferred dry mixing due to chemical stability and content uniformity issues that arise with [redacted]. (Fischer Tr. 150:10-25, 178:14-20, 183:2-16, 191:17-22.) Accordingly, the Court finds that Sun has not raised a substantial question as to validity on the written description challenge.

3. *Enablement*

Sun also argues that the asserted patents are invalid for failure to comply with 35 U.S.C. § 112(a). (ECF No. 380 at 36-41.) Pursuant to section 112(a), a patent must enable a POSA to "make and use" the claimed invention. 35 U.S.C. § 112(a). To prevail on a lack of enablement argument, "a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014) (citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988); *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) ("To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.") (citations omitted).

"[A]n enablement determination is made retrospectively, *i.e.*, by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time[.]" *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371-72 (Fed. Cir. 1999). To assess whether experimentation is "undue," courts evaluate the eight factors arising from *Wands*, 858 F.2d at 737 (the "Wands factors"). These factors consist of: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1335 (Fed. Cir. 2013) (citing *Wands*, 188 F.3d at 1371). A reasonable amount of routine experimentation is permissive. *See ALZA*, 603 F.3d at 940.

Sun argues that Orexo fails to enable the asserted claims because a POSA would not know how to use [redacted] with buprenorphine to make separate microparticles of buprenorphine and weak acid particles. (ECF No. 380 at 38.) As Sun's expert, Dr. Forrest testified, the "specification only teaches dry mixing to obtain . . . separate particles of buprenorphine and weak acid." (*Id.* (citing Forrest Tr. 987:5-10).) Sun further argues that for a POSA to use [redacted] to achieve the composition of the invention, a POSA "would have to then conduct at a minimum, for example, the pH [drip] test, and . . . potentially other tests too. And then [the POSA] would have to ultimately test for improved bioavailability[,]" which amounts to undue experimentation. (*Id.* at 39 (citing Forrest Tr. 990:8-20).)

Orexo contends that Sun's arguments fail on the law and the facts. (ECF No. 381 at 45.) Specifically, Orexo argues that the asserted claims are product claims so the disclosure of any mode of making and using the invention is sufficient to satisfy the enablement requirement. (*Id.* (citing *Invitrogen*, 429 F.3d at 1071; *AstraZeneca*, 2014 WL 2526909 at *6).) And Sun's expert, Dr. Forrest admits that making the claimed invention by dry mixing is enabled. (*Id.* (citing Forrest Tr. 977:25-978:6).) Second, Orexo argues that the proper test for undue experimentation is not "merely quantitative," and that the proper test for testing undue experimentation arises under the *Wands* factors and that Dr. Forrest provided no opinion with respect to the *Wands* factors. (*Id.* at 47.)

Again, the experts in this case do not dispute that the asserted claims in this case are composition/product claims and not process claims. Accordingly, "[t]the enablement requirement is met if the description enables any mode of making and using the invention." *Invitrogen*, 429 F.3d at 1071 (citing *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 13621 (Fed. Cir. 1998)) ("Enablement does not require the inventor to foresee every means of implementing an invention

at pains of losing his patent franchise . . . Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain."); *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991) ("The enablement requirement is met if the description enables any mode of making and using the claimed invention."); *AstraZeneca*, 2014 WL 2526909, at *6 ("For product claims, such as those asserted here by virtue of the now-governing broad claim construction, the enablement requirement is satisfied if the specification provides a single way to make the claimed product.") (emphasis omitted).

There does not appear to be a dispute that the specification enables a POSA to make the claimed invention through dry mixing without undue experimentation. First, Dr. Forrest concedes that dry mixing is not a complex process. (Forrest Tr. 977:25-978:6.) Dr. Forrest was asked:

> Q. Is dry mixing a complex process?
>
> A. Generally it's not very complex. It can take time, but in a lot of ways, you could do it -- if you had the licenses for the drug compounds, you could almost do it in a kitchen. You can do it with just a simple planetary mixer, KitchenAid. It just involves physically applying force to the dry powder over a minimum length.
>
> [(*Id.*)]

Second, Dr. Forrest testified that the asserted patents contain "extensive examples" of dry mixing. (*Id.* at 978:7-9.) Third, Dr. Forrest testified that a POSA could conduct a pH drip test of tablets that are made by dry mixing. (*Id.* at 978:10-13.) Fourth, the asserted patents contain a clinical trial on the enhanced bioavailability of Zubsolv® based on tablets that were made by dry mixing. (*Id.* at 978:18-24.) However, much like Sun's flawed written description argument, Sun reiterates the argument that the specification fails to properly disclose how to make the invention

[redacted] But the specification need only teach a single method and it has done so in this case. *Invitrogen*, 429 F.3d at 1071.

Sun asserts that the asserted patents are invalid for failure to enable the full scope of the claimed embodiments without undue experimentation. (ECF No. 380 at 37 (citing *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243 (2023)).) In *Amgen*, the plaintiff sought "to monopolize an entire class of things defined by their function—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors. The record reflects that this class of antibodies does not include just the 26 that Amgen has described by their amino acid sequences, but a 'vast' number of additional antibodies that it has not." *Amgen*, 143 S. Ct. 1256. The Federal Circuit affirmed the District Court's finding that Amgen did not properly enable a POSA to make and use the claimed antibodies beyond the scope of the 26 working examples. *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1088 (Fed. Cir. 2021). The United States Supreme Court affirmed the Federal Circuit's holding that the asserted claims attempted to encompass an entire "genus" of embodiments, and Amgen "enable[d] only a little[.]" *Amgen,* 143 S. Ct. at 1258.

Amgen reaffirmed that when a party "monopolize[s] an entire class of things defined by their function," the party must enable a POSA to make and use the entire class. *Id.* However, *Amgen* is inapposite with this case. This case involves a patent for a single composition of an opioid dependence drug, not an entire "genus." Orexo does not seek to "monopolize an entire class of things defined by their function," rather Orexo's invention is a narrow composition covering a sublingual tablet containing separate microparticles of buprenorphine and weak acid. *Id.* Since the two types of claims are different, and the breadth of the claims are different, *Amgen* is distinguishable from this case.

4. *Obviousness*

"In a challenge based on obviousness under 35 U.S.C. § 103, the person alleging invalidity must show prior art references which alone or combined with other references would have rendered the invention obvious to one of ordinary skill in the art at the time of invention." *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing 35 U.S.C. § 103). Obviousness is a question of law based on the following four underlying factual inquiries: "(1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the pertinent art,[26] and (4) secondary considerations of nonobviousness. *AstraZeneca LP v. Breath Ltd.*, 542 F. Appx. 971, 978 (Fed. Cir. 2013) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)) (internal quotations omitted). Secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented and to guard against hindsight reconstruction of references to reach the claimed invention. *KSR Int'l Co.*, 550 U.S. at 406 (citation omitted); *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1368 (Fed. Cir. 2012).

A party seeking to invalidate a patent on the basis of obviousness must "demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Kinetic Concepts*, 688 F.3d at 1360 (citation omitted). A suggestion of a motivation to combine generally arises in the references

[26] Again, prior to trial, the Court defined a POSA as a person who possess as Ph.D. in pharmaceutical sciences or related fields with one to three (1-3) years of experience in the development of pharmaceutical formulations, or, in the alternative, a person who possesses a B.S. in pharmaceutical sciences or related fields, and at least five (5) years experience in the development of pharmaceutical formulations. (ECF No. 343 at 9.)

themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those ordinary skilled in the art. *Al-Site Corp.*, 174 F.3d at 1324. "While an analysis of any teaching, suggestion, or motivation to combine elements from different prior art references is useful in an obviousness analysis, the overall inquiry must be expansive and flexible." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citing *KSR Int'l Co.*, 550 U.S. at 415)).

Here, claims 2 and 16 from the '900 patent and claims 6 and 13 from the '387 patent, which depend on claim 1 generally require: (1) a sublingual tablet comprising buprenorphine in the form of microparticles, (2) a weak acid in which the particles are separate from the microparticles of buprenorphine, (3) a disintegrant, (4) naloxone, (5) specific doses of buprenorphine, and (6) a ratio of buprenorphine to naloxone of 4 to 1. (JTX-0003, JTX-0005; Crowley Tr. 1022:9-1023:4.) Some of the asserted claims require an associative admixture, a specific tablet weight, a specific tablet hardness, and a specific disintegrant group. (Crowley Tr. 1023:8-10.)

i. <u>*Scope and Content of Prior Art*</u>

Sun argues that the asserted claims would have been obvious to a POSA as of September 19, 2011, the priority date for the asserted patents because there was a wealth of information reported in technical literature relating to buprenorphine and naloxone formulations used to treat opioid addiction, namely Vanderbist, Pettersson '443, Chapleo, and Suboxone® PI/Cairns. (ECF No. 380 at 43-44 (citing Crowley Tr. 1025:4-13).) Sun asserts that although Vanderbist and Chapleo were provided to the examiner during prosecution, the examiner never cited nor referenced this prior art nor were they considered in the previous litigation involving the validity of the '330 patent. (*Id.* at 44 (citing *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265 (Fed. Cir. 2018).)

Sun contends that combining the teachings of Vanderbist and Pettersson '443 leads to the claimed invention because Example 2 of Vanderbist discloses a dry mixing process for a tablet having buprenorphine with, among other ingredients, citric acid (weak acid) and Pettersson '443 provides express motivation to use microparticles of buprenorphine and a disintegrant to increase the dissolution rate, which can ultimately increase bioavailability. (*Id.* at 44-45 (citing DTX-0045 and DTX-0057).) Sun further contends that the prior art specifically taught that adding citric acid to an opioid-tablet formulation causes a pH-timing effect that increases bioavailability of the opioid. (*Id.* at 46 (citing DTX-0068).) Finally, Sun submits that the remaining limitations (ratio of buprenorphine to naloxone and doses of buprenorphine, tablet weight, associative admixture, and tablet hardness) were not novel and would have been obvious to a POSA. (*Id.* at 47-48.)

In response, Orexo argues that the Court should reject Sun's obviousness argument because the prior art referenced by Sun has already been considered and rejected by the examiner and the Federal Circuit. (ECF No. 381 at 31.) Moreover, Orexo argues that Sun's prior art references are missing at least two limitations recited in the asserted claims. (*Id.* at 32.) claims 6 and 13 of the '387 patent both recite hardness (or crushing strength) in a range of "about 15N to about 50N" and all asserted claims recite highly specific buprenorphine dosages, including 11.4, 8.6, 5.7, 2.9 and 1.4 mg. (*Id.* (citing JTX-0005.0026; Crowley Tr. 1074:6-13).) Finally, Orexo argues that a POSA would not be motivated to combine the prior art and would not have had a reasonable expectation of success of increasing bioavailability. (ECF No. 381 at 33-34.) Orexo relies on the Federal Circuit's ruling in *Orexo AB* where the Court held that there was "no suggestion that the specified elements should be selected and combined" and the examiner's finding that there "was no clear guidance in the prior art on how to accomplish improved buprenorphine bioavailability in a sublingual tablet." (*Id.* (citing *Orexo AB*, 903 F.3d at 1273; JTX-0008.1411, JTX-0011.0171).)

To properly determine whether a POSA would have been motivated by the prior art to obtain the claimed formulations of the asserted patents with a reasonable expectation of success, the Court must evaluate the scope and content of Sun's combination references. As such, the Court will evaluate each prior art reference in turn.

a. Vanderbist

Vanderbist, is an international patent application titled, "Stable Oral Pharmaceutical Compositions of Buprenorphine and Derivatives," which was published on December 15, 2005, before the priority date of the asserted patents. (DTX-0057.0001.) Vanderbist "describes stable oral compositions of buprenorphine or salt thereof" as well as "manufacturing processes to obtain said compositions." (*Id.* at 0002.) Example 2 of Vanderbist describes the manufacturing of tablets of buprenorphine using direct compression and mixing citric acid and sodium citrate in a planetary mixer. (*Id.* at 0013-0014; Crowley Tr. 1042:10-16.) Additionally, Vanderbist discloses that "citric acid is used in the compositions as a pH modifier agent" and that "a second active ingredient" may be used as an opioid antagonist such as naloxone. (DTX-0057.0005, 0008.) Vanderbist was among the list of references considered by the Patent Office during prosecution of the asserted patents. (Crowley Tr. 1041:18-21.)

Sun presented testimony from Michael Crowley, Ph.D., an expert in pharmaceutical sciences, including in the formulation and manufacture of tablet formulations on the issue of obviousness. (Crowley Tr. 1021:15-21.) Dr. Crowley testified that Vanderbist discloses stable oral compositions of buprenorphine in the form of sublingual tablets that can include citric acid as a pH modifier and can be administered with naloxone. (*Id.* at 1042:2-6.) Dr. Crowley further explained that Example 2 of Vanderbist discloses a dry mixing process, which results in separate particles. (*Id.* at 1042:12-16; 1068:23-25.) Dr. Crowley testified that "[s]o you can see they are

just simply mixed together and then directly compressed into a tablet. Separate and distinct particles go in; separate and distinct particles remain." (*Id.* at 1043:3-9.) Dr. Crowley acknowledged that Vanderbist is silent with respect to buprenorphine particle size, but that micronizing was well-known in the art. (*Id.* at 1043:12-17, 1069:23-1070:3, 1089:22-1090:1.) He also acknowledged that Vanderbist does not disclose using a "superdisintegrant" such as croscarmellose sodium, crospovidone, or sodium starch glycolate as disclosed in claim 1 of the asserted patents. (*Id.* at 1072:3-6.) Finally, Dr. Crowley testified on cross-examination that Example 2 does not disclose the pharmacokinetics or improved bioavailability of the tablets. (*Id.* at 1072:7-18.)

Orexo's expert, Dr. Davies testified that separate microparticles of buprenorphine and particles of weak acid are not understood to result from Vanderbist because Vanderbist is silent with respect to particle size. (Davies Tr. 1113:2-11.) Dr. Davies also testified that hardness is not achieved by routine experimentation because "to achieve a particular crushing strength, you have to do experimental work, and it is an inherent property of a formulation" and it was very difficult to manufacture the tablets disclosed in Example 2 of Vanderbist. (*Id.* at 1113:12-25 (referring to testimony from Sun's expert, Mary M. Dothage, who was asked to replicate the Vanderbist examples and testified that 75% of the tablets that were made chipped); Dothage Tr. 706:12-19.) On cross-examination, Dr. Davies agreed that the nature of those particulate ingredients in Vanderbist Example 2 will be preserved during the manufacturing process because the process does not include a solvent. (Davies Tr. 1207:4-15.)

b. *Pettersson '443*

U.S. Patent No. 129,443 ("Pettersson '443") titled "Non-Abusable Pharmaceutical Composition Comprising Opioids" was published on May 27, 2010, before the priority date of the

asserted patents. (DTX-0045.0001.) Pettersson '443 "relates to new, fact acting, non-abusable pharmaceutical compositions that are useful in the treatment of pain, which compositions may be administered transmucosally and in particular sublingually." (*Id.* at 0002.) Pettersson '443 discloses that "[p]resently-available oral, rectal, and sublingual opioid analgesic formulations have relatively lengthy onset times and/or erratic absorption characteristics, which makes them not entirely suitable for the control of acute and/or breakthrough pain." (*Id.*) Therefore, at the time Pettersson '443 was published, there was "a real and growing clinical need for fast-acting orally-delivered drug compositions comprising opioid analgesics." (*Id.*)

Pettersson '443 discloses that "[t]he compositions of the invention may also have the advantage that they substantially reduce the degree of absorption of active ingredients via swallowed saliva, as well as enabling the administration of 'reduced' amounts of the opioid analgesic active ingredient that is employed, so substantially reducing the risk of side effects, as well as intra- and interpatient variability of therapeutic response." (*Id.* at 0007.) Pettersson '443 states:

> "[t]he compositions of the invention are interactive mixtures. The term "interactive" mixture will be understood by those skilled in the art to denote a mixture in which particles do not appear as single units, as in random mixtures, but rather where smaller particles (of, for example, opioid analgesic and/or bioadhesion and/or mucoadhesion promoting agent) are attached to (i.e. adhered to or associated with) the surfaces of larger opioid antagonist-containing, or opioid antagonist-based, carrier particles. Such mixtures are characterized by interactive forces (for example van der Waals forces, electrostatic or Coulombic forces, and/or hydrogen bonding) between carrier and surface-associated particles. [] In the final mixture, the interactive forces need to be strong enough to keep the adherent particles at the carrier surface, in order to create a homogeneous mixture.
>
> [(*Id.* at 0003.)]

Furthermore, Pettersson '443 discloses that compositions of the invention may have a better pharmacokinetic profile and that the "[o]pioid analgesic active ingredients in the compositions of the invention are preferably in the form of microparticles, preferably with a weight based mean diameter of between about 0.5 μm and about 15 μm, such as about 1 μm and about 10 μm." (*Id.* at 0007 and 0004.) A disintegrant may also be in the composition of the invention, especially if tablets for sublingual administration are used, such as cross-linked polyvinylpyrrolidone, carboxymethyl starch, and natural starch. (*Id.* at 0005.) Pettersson '443 discusses dry mixing and states: "in one embodiment, particles of opioid analgesic may be dry mixed with opioid antagonist-containing carrier particles over a period of time that is sufficiently long to enable appropriate amounts of active ingredients to adhere to the surface of the carrier particles[.]" (*Id.* at 0006.) Pettersson '443 teaches that the final tablets are in a weight range of about 30 to about 400 mg, but preferably between about 60 and about 160 mg. (*Id.*) Pettersson '443 was also considered by the Patent Examiner. (Crowley Tr. 1074:19-23.)

Sun asserts that a POSA reading the disclosures of Pettersson '443 would understand that opiate formulations were being abused and that "[t]echniques to increase bioavailability would present a reduce dose of the opiate and provide a safer side effect profile." (Crowley Tr. 1045:25-1046:10.) Dr. Crowley testified that Pettersson '443 teaches a means to achieve increased bioavailability, which is by "an ordered mixture or interactive mixture using microparticles of the drug substance and disintegrants, specifically some super disintegrants, like crosPVP, and finally provides ideal tablet weights." (*Id.*) However, on cross-examination, Dr. Crowley acknowledged that the Pettersson '443 disclosure does not include a weak acid, provides no PK or pharmacokinetics data, and that all of the examples in Pettersson '443 relate to fentanyl and not buprenorphine. (*Id.* at 1075:4-1076:23.)

c. *Chapleo*

U.S. Patent No. 168,147 ("Chapleo") titled "Medicinal Compositions Comprising Buprenorphine and Naloxone" was published on July 1, 2010, which was before the priority date of the asserted patents. (DTX-0046.0001.) Chapleo provides a composition for the treatment of pain in human patients wherein said composition comprises buprenorphine to naloxone in a ratio by weight of 2:1 to 8:1, the amount of buprenorphine and naloxone being suitable to provide analgesia, the composition being in a transdermal or transmucosal dosage form. (*Id.*) Additionally, Chapleo discloses some of the side effects of buprenorphine such as "nausea and vomiting, constipation and respiratory depression[.]" (*Id.* at 0002.)

With respect to the dosage of buprenorphine, Chapleo discloses that the "compositions of the present invention may contain any amount of buprenorphine, up to the upper end of conventional clinical practice. Suitably, they may contain up to 32 mg buprenorphine per unit dose," which would include the doses in the asserted claims. (*Id.* at 0003; Crowley Tr. 1047:15-17.) Orexo asserts this reference is insufficient as it does not disclose the specific buprenorphine dosage amounts that are shown in the asserted patents. (Davies Tr. 1114:13-22.)

Chapleo further explains that compositions of the invention "may contain a buffer system, for example an organic acid and a salt thereof, such as citric acid and sodium citrate." (DTX-0046.0003.) Finally, Chapleo discloses that the "[c]ompositions for use in the method in the form of lozenges and tablets suitably" contain "granulating and disintegrating agents selected from materials such as starch, binding agents such as povidone or hydroxypropylmethyl cellulose and lubricating agents such as magnesium stearate." (*Id.*) Chapleo was among the list of references considered by the Patent Office during prosecution of the asserted patents. (Crowley Tr. 1046:17-20.)

d. Cairns

Cairns is an international patent application titled "Pack," which was published on December 18, 2008, before the priority date of the asserted patents. (DTX-0058.0001.) Cairns describes Suboxone®, which are sublingual tablets containing "up to 20 mg of buprenorphine, preferably up to 16 mg, preferably up to 12 mg" and a co-active ingredient such as naloxone. (*Id.* at 0004.) The "weight ratio in the tablet of buprenorphine to such a co-active ingredient, or of co-active ingredients in total, is preferably in the range of 2:1 to 8:1, preferably 3:1 to 5:1," which includes the claimed 4:1 ratio. (*Id.* at 0004-0005.) Cairns discloses that "[p]referably, the tablets comprise a mixture of anhydrous citric acid and sodium citrate[,]" and that they preferably comprise a disintegrant such as sodium croscarmellose, maize starch, or crospovidone. (*Id.* at 0005-0006.) Cairns was also considered by the Patent Office during prosecution of the asserted patents as the closest prior art. (JTX-0008.1410.)

e. Suboxone® PI

Suboxone® PI[27] was published in 2002, before the priority date of the asserted patents. (DTX-0027.0049.) Suboxone® PI describes the Suboxone® sublingual tablet at two dosage strengths: 2 mg of buprenorphine with 0.5 mg naloxone, and 8 mg buprenorphine with 2 mg naloxone. (*Id.* at 0002.) Suboxone® PI teaches that each tablet "also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No. 6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon/lime flavor." (*Id.*) Suboxone® PDR[28], which is the equivalent to Suboxone® PI was considered before allowing the claims of the asserted patents. (Crowley Tr. 1065:3-9.)

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[27] Suboxone® PI refers to Suboxone prescribing information. (Crowley Tr. 1064:12-14.)

[28] Suboxone® PDR refers to Physicians Desk Reference. (Crowley Tr. 1065:3-6.)

ii. Differences Between Prior Art and Claims at Issue

Orexo argues that Sun has failed to carry its burden of proving obviousness because Sun has failed to prove that all of the limitations in the asserted claims are disclosed in Sun's combination references and that a POSA, as of 2011, would not have been motivated to improve bioavailability of buprenorphine formulations because "there was no clear guidance in the prior art on how to accomplish the improved bioavailability in a sublingual tablet." (Davies Tr. 1114:23-1115:5; JTX-0008.1411.) For example, Orexo contends that Vanderbist does not disclose separate buprenorphine microparticles and weak acid particles, as there is no disclosure of particle size. Orexo also contends that the prior art references are missing the tablet hardness limitation (or crushing strength) of 15N to about 50N as disclosed in claims 6 and 13 of the '387 patent, which Sun's expert does not deny. (Crowley Tr. 1077:2-4.) Dr. Davies testified that hardness cannot be achieved by routine experimentation. (Davies Tr. 1113:12-1114:3.) Dr. Davies explained that "to achieve a particular crushing strength, you have to do experimental work, and it is an inherent property of a formulation." (*Id.* at 1113:12-25.)

Moreover, Orexo contends that the prior art references do not disclose the dosage strength limitation. (Davies Tr. 1114:13-22.) Claims 2 and 16 of the '900 patent both recite buprenorphine dosages of 11.4, 8.6, 5.7, 2.9 or 1.4 mg and Dr. Crowley admitted that those dosage strengths are not explicitly recited in the prior art. (Crowley Tr. 1074:5-13.) Orexo contends that Dr. Crowley provided no explanation as to why a POSA would choose, down to the decimal point, those dosage strengths and those precise dosage strengths resulted in an unexpected 66% increase in bioavailability relative to Suboxone® tablets. (Davies Tr. 1114:13-22, 1127:3:13; Fischer Tr. 141:8-24.)

Finally, Orexo submits that a POSA would not have been motivated to improve the bioavailability of buprenorphine by micronizing the drug substance and using a disintegrant because of POSA would have expected that combining those technologies would result in buprenorphine being swallowed instead of being absorbed. Orexo's expert, Dr. Davies acknowledges that Pettersson '443 provides the ordered mixture technology, but he claims that a POSA would not be motivated to combine Pettersson '443's ordered mixture technology with the citric acid technology disclosed in the prior art because it would result in buprenorphine being swallowed instead of being absorbed. (Davies Tr. 1115:15-21.) Dr. Davies explained that combining a weak acid and an ordered mixture technology leads to buprenorphine dissolving too rapidly causing it to be swallowed rather than absorbed. (*Id.* at 1116:2-21.) Dr. Davies further explained that absorption is important because it will allow the buprenorphine to pass through the liver and out to the body, which is referred to as the "first pass effect." (*Id.* at 1116:11-1117:10.) Dr. Davies testified that this issue was noted in the prior art and the asserted patents and that one would expect that lowering the pH would give rise to more buprenorphine in an ionized state at the site of absorption, which would in turn be expected to decrease the degree of absorption across the sublingual mucosa. (*Id.* at 1118:19-1119:22; JTX-0001.0020.)

In response, Sun contends that the prior art discloses each of the elements in all asserted claims.[29] (Crowley Tr. 1049:22-1050:13.) Sun submits that buprenorphine microparticles are disclosed in Pettersson '443, the use of weak acid particles and citric acid is taught in Vanderbist and Chapleo, and buprenorphine being separate and distinct from the weak acid is disclosed in

[29] Dr. Crowley testified that the standard of obviousness is "that the differences between the prior art and a patent claim are obvious when the prior art discloses each element of the claim; that there is a motivation to combine the disclosed elements in order to arrive at the claimed invention; and that there was a reasonable expectation of success." (Crowley Tr. 1049:12-19.)

Example 2 of Vanderbist. (*Id.* at 1049:22-1050:8.) As for the remaining limitations (*i.e.*, the specific use of a disintegrant, tablet hardness, using an associative admixture, or tablet weight) Sun contends that they were not new approaches to a POSA as of 2011 in light of the prior art. (Crowley Tr. 1055:5-12.) Dr. Crowley contends that specific hardness and crushing strength can be achieved by routine experimentation. (Crowley Tr. 1053:13-20.) Dr. Crowley testified that "[i]t is routine that when you're compressing a tablet, the two most simple knobs on that machine are the precompression force and the main compression force." (*Id.* at 1088:21-1089:12.) Dr. Crowley stated that the hardness and crushing strength claimed in the asserted patents "are very common and achievable for tablets." (*Id.* at 1092:12-15.) As for dosage strength, Dr. Crowley admitted that Chapleo does not explicitly disclose the buprenorphine dosage strengths but does teach that you can administer up to 32 mgs of buprenorphine in his compositions. (*Id.* at 1047:13-17.)

Moreover, Sun contends that a POSA would have been motivated to increase the bioavailability of buprenorphine formulations as it was a primary objective of many drug development efforts as it would enable the use of a lower dose, potentially reducing known harmful side effects and an opportunity for cost savings. (*Id.* at 1050:16-23.) Dr. Crowley testified that a POSA would be motivated to micronize the drug substance and use disintegrants in the tablet formulations, which were well known approaches to increase bioavailability. (*Id.* at 1050:24-1051:9.)

Finally, Sun contends that a POSA would have had a reasonable expectation of success in improving bioavailability using microparticles and disintegrants. (*Id.* at 1051:12-18.) Dr. Crowley testified that the "use of microparticles and disintegrants were well-known techniques in order to achieve" improved bioavailability. (*Id.* at 1051:19-1052:4.) Dr. Crowley also testified that based

on the teachings of the prior art, a POSA would expect a citric acid buffer system would increase bioavailability as well. (*Id.* at 1057:1-14.) Dr. Crowley explained that a leading article from 2006 titled, Fentanyl Effervescent Buccal Tablets, by Steven Durfee ("Durfee") taught that the use of citric acid and sodium citrate results in a pH timing effect that was "very useful to increase the bioavailability of fentanyl." (*Id.* at 1057:2-11; DTX-0068.0003-0004.)

The Court finds that Sun has not met its burden in demonstrating obviousness by clear and convincing evidence. First, there is no dispute that Sun's combined references, Vanderbist, Pettersson '443, Chapleo, Cairns, and a substantially equivalent reference to Suboxone® PI were among the list of references considered by the Patent Office during prosecution of the asserted patents. (Crowley Tr. 1041:18-21, 1074:19-23, 1046:17-20, 1065:3-9; JTX-0008.1410.) Not only is there a "presumption that the Examiner did his duty and knew what claims he was allowing[,]" but the "burden is especially difficult when the prior art was before the PTO examiner during prosecution of the application." *Al-Site Corp.*, 174 F.3d at 1323 (citation omitted).

Second, the Court finds that Sun has not demonstrated that all claim limitations are found in the prior art references. "To establish obviousness, the prior art must teach or suggest all claim limitations of the patent in question[.]" *Cy Technology Group LLC v. Groupon, Inc.*, Civ. No. 10-7287, 2011 WL 13193420 at *2 (D.C. Cal. July 7, 2011) (citing *KSR Int'l Co.*, 550 U.S. at 406)). The Court finds that Vanderbist Example 2 does not teach a weak acid in which the particles are separate from the *microparticles* of buprenorphine as disclosed in claim 1 of the asserted patents. The parties do not dispute that Vanderbist is silent with regards to microparticles or the size of the buprenorphine particles. (Crowley Tr. 1043:12-17, 1069:23-1070:3, 1089:22-1090:1.) Indeed, Dr. Crowley testified that a POSA would have to make at least three modifications to Vanderbist in order to achieve the claimed invention (increasing the dissolution rate of buprenorphine and

improving bioavailability): (1) use buprenorphine microparticles; (2) incorporate buprenorphine into an ordered mixture; and (3) add a superdisintegrant. (*Id.* at 1077:24-1079:10.)

Also, the prior art does not cite the specific buprenorphine dosage strengths (11.4, 8.6, 5.7, 2.9 or 1.4 mg) as disclosed in claims 2 and 16 of the '900 patent or the hardness limitation (or crushing strength) of 15N to about 50N as disclosed in claims 6 and 13 of the '387 patent. Dr. Crowley admitted that the specific dosage strengths are not explicitly recited in the prior art and that he did not cite any prior art references that disclosed the claimed crushing strength, nor did he offer any opinions about a motivation to achieve the claimed crushing strength values in particular. (Crowley Tr. 1077:2-4, 1074:5-13.) The Court finds that Chapleo's reference that you can administer up to 32 mg of buprenorphine or that the hardness and crushing strength are "very common and achievable for tablets" does not satisfy Sun's burden of proving obviousness by clear and convincing evidence and protect against hindsight claims of obviousness. *In re Cyclobenzaprine*, 676 F.3d at 1071 (holding that where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, courts should reject hindsight claims of obviousness); (*see also* Fischer Tr. 186:5-11 ("it's not just turning the . . . machine to get another hardness. It's sometimes the hardness flattens out and starts to go down again, if you – and that depends on the composition and the binding properties of it.").)

With respect to motivation to combine prior art, as of 2011 there was an opioid crisis in the United States and the diversion and illicit use of Suboxone® was frequently reported. (DeLuca Tr. 87:9-89:12; JTX-0001.0013.) As such, there was a "clinical need for an abuse-resistant product for use in opioid addiction substitution therapy" with "increase[ed] [] bioavailability of buprenorphine" such that "it might be possible to reduce the amount of [buprenorphine], giving

rise to less opioid in the formulation and so reducing the amount available for injection if diverted by way of intravenous abuse." (JTX-0001.0013.) While micronization and the use of disintegrants to improve dissolution may have been well known in the prior art, Sun has not established by clear and convincing evidence that a POSA would be motivated to combine the prior art to achieve the claimed invention with a reasonable expectation of success.

As noted by the examiner "there was no clear guidance in the prior art on how to accomplish improved buprenorphine bioavailability in a sublingual tablet. (JTX-0008.1411 (emphasis in original).) This was "particularly evident in view of Applicant's demonstration that the mere presence of citric acid in the sublingual tablets or sublingual film strips formulated according to the prior art (e.g., Cairns or Myers) is sufficient to achieve the superior pharmacokinetic profile exhibited by the instant invention (e.g., example 5; figures 5-6 and example 9; figures 8 and 9 of the instant specification)." (*Id.*)

Sun contends that Durfee teaches that the use of citric acid and sodium citrate results in a pH timing effect that was "very useful to increase the bioavailability of fentanyl." (DTX-0068.0003-0004.) Dr. Crowley testified that Durfee used a "dynamic pH shift," which facilitated the "dissolution of the fentanyl, and then by increasing the pH back up, it promoted absorption" thereby resulting in improved bioavailability. (Crowley Tr. 1037:11-18.) According to Dr. Crowley's testimony, fentanyl and buprenorphine are both opioids with similar pKa's. (*Id*. at 1057: 2-11.) They are also both weak bases, lipophilic, and exhibit poor water solubility, which makes them good candidates for buccal or transmucosal administration and absorption. (*Id.*) Sun submits that a POSA would understand the disclosure in Durfee to disclose a pH timing effect that would have a significant increase in bioavailability. (*Id.* at 1038:16-18, 1040:12-16.)

Dr. Davies, on the other hand, testified that Durfee would not motivate a POSA to combine because it does not cite buprenorphine microparticles separate to weak acid particles. (Davies Tr. 1122:16-21.) Dr. Davies further explained that Durfee is a publication based on a different drug, fentanyl, a different kind of dosage form, buccal versus sublingual administration, and it involves effervescent tablets. (*Id.* at 1124:1-6.) Dr. Davies stated that "all of those contribute to the fact that this is different to the claimed invention." (*Id.* at 1124:7-8.)

Durfee teaches a new fentanyl oral mucosal delivery system involving a buccal tablet[30] that increases the rate and efficiency of fentanyl absorption. (DTX-0068.0001). Durfee also teaches that the enhanced absorption is caused by a dynamic shift in pH in the microenvironment surrounding the tablet. (*Id.*) Specifically, Durfee instructs that:

> "[i]n an effort to increase the efficacy of fentanyl buccal absorption, a system was developed that enables a tablet, when placed within the buccal cavity, to produce dynamic shifts in pH to facilitate the dissolution and then the absorption of fentanyl. An initial reduction in pH within the microenvironment where the formulation makes contact with the buccal mucosa favors dissolution of ionized fentanyl. Once this fentanyl is dissolved, an increasing pH begins to favor the nonionized fentanyl, which as it forms, can be readily absorbed. Therefore, the extent and speed of fentanyl absorption across the buccal mucosa are increased as a result of this dynamic process."
>
> [(*Id.* at 0002.)]

While Durfee discloses the use of citric acid to reduce pH, an effervescent reaction is used in Durfee to achieve the pH timing and it does not disclose buprenorphine microparticles separate to weak acid particles. (Crowley Tr. 1039:3-4; 1039:15-23 (testifying that the Durfee report

[30] The Court notes that a buccal tablet is different than a sublingual tablet. A buccal tablet is administered on the buccal mucosa, which is between the cheek and the gum. (Crowley Tr. 1082:10-11.) A sublingual tablet is administered below the tongue. (*See* Davies Tr. 1124:3-1125:3.)

discloses a pH timing effect resulting in significantly greater bioavailability and exposure compared to a tablet without the effervescent reaction); Davies Tr. 1122:16-21 (testifying that Durfee would not motivate a POSA to combine because it does not cite buprenorphine microparticles separate to weak acid particles).) An effervescent reaction works differently than Zubsolv® in that the weak acid reacts with bicarbonate "and you get a fizzing reaction." (Crowley Tr. 1082:21-5.) In other words, bubbles are created as carbon dioxide is liberated from the chemical reaction. (*Id.*; DTX-0068.0004 (stating "As the CO2 produced in the effervescence reaction described above began to dissipate, the mean pH increased back toward baseline.").) Also, the chemical structure of fentanyl and buprenorphine are different, and fentanyl is more potent than buprenorphine, which means there's much less drug in a fentanyl tablet. (Crowley Tr. at 1084:14-1085:3.) Therefore, while Durfee teaches that citric acid may cause greater absorption due to a pH timing, the Court is not convinced that it would teach a POSA how to achieve the superior pharmacokinetic profile shown in the asserted patents by use of separate microparticles of buprenorphine and weak acids with reasonable success.

The Court further finds that Vanderbist Example 2 would not motivate a POSA to combine to get separate and distinct buprenorphine microparticles and a weak acid as claimed in the asserted patents with reasonable success. Again, Vanderbist is silent with respect to the size of the buprenorphine particles and Dr. Crowley acknowledged that a POSA would need to make at least three modifications to Vanderbist in order to achieve the claimed invention – (1) create microparticles, (2) incorporate buprenorphine into an ordered mixture, and (3) add a superdisintegrant, all of which would increase the dissolution of buprenorphine and its bioavailability. (*Id.* at 1077:24-1079:10; Davies Tr. 1121: 11-16 (testifying that "[o]rdered mixtures and weak acids have been around quite a while, but nobody has ever combined them in

a formulation for a sublingual tablet.").) Therefore, the Court cannot find that Sun has established by clear and convincing evidence that a POSA would have been motivated to combine the prior art to arrive at the claimed invention and would have had a reasonable expectation of success in achieving the invention. *See Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (stating that a finding of obviousness requires the moving party to demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention and that a skilled artisan would have had a reasonable expectation of success in combining the prior art.)

iii. *Secondary Considerations (Objective Indicia)*

Objective indicia constitute "independent evidence of nonobviousness." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). Indeed, objective indicia "may often be the most probative and cogent evidence of nonobviousness in the record." *Id.* (citing *Ortho-McNeil Pharm v. Mylan Labs, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008)). Such evidence "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Id.* (citing *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573 (Fed. Cir. 1984)). Objective indicia also "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)). Orexo, as the patentee, bears the burden of proving a nexus between the evidence of secondary considerations and the asserted patents. *Fox Factory v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (citation omitted).

Orexo contends that the unexpectedly improved bioavailability relative to Suboxone® tablets, the unexpected patient preference over Suboxone® tablets and film and industry praise are

all objective indicia that supports nonobviousness. (ECF No. 381 at 36-39.) The Court will address each of these secondary considerations in turn.

a. Unexpected Improved Bioavailability

Orexo contends that the unexpectedly improved bioavailability of Zubsolv® supports nonobviousness of the asserted claims. Specifically, Dr. Davies testified:

> "[i]t's the unexpected result of combining a weak acid and an ordered mixture, which increases dissolution and also increases absorption. And it's because you have these separate buprenorphine and weak acid particles that promote buprenorphine dissolution and absorption. And that bioavailability increase of 66 percent relative to Suboxone tablets is the consequence of having separate buprenorphine and weak acid particles."
>
> [(Davies Tr. 1127:6-13.)]

Example 2 of the asserted patents shows a 66% improvement in bioavailability of buprenorphine, and Examples 7 and 8 of the patent show bioequivalent results for a sublingual tablet containing 29% less buprenorphine than in Suboxone® tablets.[31] (JTX-0001.0022, Ex. 2; Davies Tr. 1127:2-18; *Orexo AB*, 903 F.3d at 1268. Further, Orexo cites to the Examiner's statement of reasons for allowance in which the Examiner notes that the "Applicant has persuasively demonstrated that the instant tablet exhibits unexpectedly superior sublingual buprenorphine bioavailability due to the

[31] Sun raises an argument that despite Zubsolv's® improved bioavailability, Zubsolv® is not more abuse deterrent than Suboxone®. Sun cites to the FDA's denial of Orexo's request to include on Zubsolv's® label the public health advantages that would result by reducing the overall amount of buprenorphine for misuse in the United States market. (DTX-0136.0056.) This issue does not impact the Court's analysis. The asserted patents clearly provide that there was a 66% increased bioavailability that resulted in a sublingual tablet containing 29% less buprenorphine than in Suboxone® tablets related to the increased bioavailability in the claimed invention. Moreover, Sun does not refute Orexo's contention that Orexo later obtained clinical evidence in the OX219-006 study (the "006 study") that Zubsolv® reduces misuse and diversion compared to Suboxone® film in opioid dependent patients. (Sumner Tr. 287:15-288:1.)

ingredients as well as the structural characteristics recited in the instant claims." (*See, e.g.*, JTX-0008.1411; Davies Tr. 1130:18-1131:21.)

Sun refutes Orexo's assertion and claims that the increased bioavailability is known and is the expected result of using microparticles, ordered mixtures, and citric acid. (Crowley Tr. 1061: 12-25.) Specifically, Sun argues that the combination of the prior art discloses the use of buprenorphine microparticles in an ordered mixture with a disintegrant, which increases dissolution and bioavailability and that citric acid results in a "dynamic pH shift," which also results in greater bioavailability. (Crowley Tr. 1061:12-25, 1025:20-25, 1033:14-23, 1035:1-1036:20, 1036:24-1037:18, 1044:8-1046:10.) Again, Sun primarily relies on Durfee to assert that the increased bioavailability would not be unexpected because Durfee teaches that adding citric acid results in greater absorption and not swallowing as claimed by Dr. Davies. (*Id.* at 1056:7-1057:14.)

The Court agrees that Zubsolv's® increased bioavailability of 66% was unexpected and that there is a nexus between the increased bioavailability and the claimed invention. For the reasons set forth above, the Court does not find that the teachings of the prior art, including Durfee would have led a POSA to combine separate buprenorphine microparticles with weak acid particles with a reasonable success of 66% increased bioavailability. As noted by the Examiner, the unexpected bioavailability is not solely due to the ingredients or use of citric acid, but also the result of "the structural characteristics recited in the instant claims." (JTX-0008.1411; JTX-0011.0171.) Not only does Durfee not disclose combining buprenorphine microparticles and a weak acid in an ordered mixture, but Sun also has not demonstrated prior art disclosing the specific dose of buprenorphine or the hardness of the tablets. Therefore, the Court finds that Zubsolv®'s

unique composition resulting in a 66% increase of buprenorphine bioavailability was not an expected result based on the Court's review of the prior art.

b. Unexpected Patient Preference over Suboxone® Tablets and Film

Orexo next argues that the unexpected patient preference for Zubsolv® over Suboxone® tablets and film supports their non-obvious argument. (Davies Tr. 1134:12-18.) Orexo presented testimony from Michael John Sumner, BM, BS, who was Chief Medical Officer for Orexo from August 2013 to June 2022. (Sumner Tr. 143:19-24.) Dr. Sumner is a UK-trained physician who practiced hospital medicine in the United Kingdom for five years. (*Id.* at 244:3-8.) Dr. Sumner provided testimony about Orexo's clinical studies, namely Orexo's Clinical Study OX219-003 (the "003 study"), which examined patient preference against Suboxone® tablets and Orexo's Clinical Study OX219-006 ("the 006 study"), which examined patient preference against Suboxone® film. (Sumner Tr. 248:12-252:25, 253:18-255:18; PTX-0085.0017, PTX-0160.0044, 0065.) Dr. Sumner testified that the 003 study found that Zubsolv® exhibited an improved taste, faster dissolution time by five to ten minutes, and a greater patient experience which they claim resulted in nearly 80% of patients preferring Zubsolv®. (Sumner Tr. 250:17-252:5 (also testifying that buprenorphine and naloxone are very bitter), 253:1-17; PTX-0085.0028, 0060.) As for the 006 study, Dr. Sumner testified "that against every parameter that we measured, Zubsolv® achieved statistical significance over Suboxone film." (Sumner Tr. 255:22-256:7; PTX-0160.0160.) Orexo contends that patient preference for Zubsolv® over Suboxone® tablets was also reported in the literature. (PTX-0157.0001.)

Dr. Davies testified that there is a nexus between the patient preference data and the asserted claims because the factors underlying patient preference – such as improved bioavailability and faster dissolve times are related to the structural characteristics of the claims –

separate buprenorphine microparticles from the weak acid particles and the use of a superdisintegrant. (Davies Tr. 1133:16-1134:18.)

Sun refutes Orexo's argument by arguing that Orexo does not cite to any academic literature or testimony from a clinical expert that supports their position that patients prefer Zubsolv® over Suboxone® tablets and film due to improved taste, mouth feel, and dissolution. Sun further contends that in a 2013 article written by inventor Fischer, he states that the improved taste may be due to the sucralose and methanol included in Zubsolv's® formulation, neither of which are claimed excipients. (DTX-0089.0004 ("The improved taste of [Zubsolv] may be attributed at least in part to the use of sucralose and menthol for taste masking of the bitter active ingredients in the [Zubsolv] formulation. For example, sucralose has a higher sweetness potency and a lower degree of bitter aftertaste than acesulfame K present in the Suboxone formulations.").)

Sun also presented testimony from Eric M. Wexler, M.D., Ph.D., a psychiatrist and medical director who treats patients who suffer from opioid dependence. (Wexler Tr.; 16:16-17:4; 20:1-6.) Dr. Wexler testified that approximately ninety percent of his prescriptions for maintenance therapy are for generic Suboxone®. (*Id.* at 68:7-10.) Dr. Wexler testified that in his experience, he prescribes generic Suboxone® in approximately 90 percent of his patients "because it is less expensive and has the same therapeutic efficacy as Zubsolv®. I have never prescribed Zubsolv® over Suboxone® based on a purportedly better taste, mouthfeel, or dissolution time, let alone improved bioavailability." (*Id.* at 124:22-125:5.) However, Dr. Wexler acknowledged that he has never formally compared Zubsolv® and Suboxone® with respect to taste, mouthfeel, or dissolution time nor has he asked his patients to make such a comparison. (*Id.* at 131:16-20; 133:16-19.) Finally, Sun contends that any patient preference claimed by Orexo is not sufficient enough to result in patient demand and change Suboxone's® control of the market. (Sumner Tr.

281:22-284:6; DTX-0153.0001 (Orexo PowerPoint noting that "[p]atient preference not sufficient to break existing monopoly – Limited patient demand for Zubsolv and most likely awareness.").)

Orexo's clinical studies appear to indicate a patient preference for Zubsolv® as compared to Suboxone® tablets and film. Sun does not dispute or refute the results of those studies. Instead, Sun relies on the testimony of Dr. Wexler; however, Dr. Wexler admitted that he never formally compared Zubsolv® and Suboxone® with respect to taste, mouthfeel or dissolution time nor has he asked his patients to make such a comparison. (Wexler Tr. 131:19-20.) Instead, costs appear to be the driving factor for Dr. Wexler prescribing Suboxone® over Zubsolv®, not a lack of patient preference. (*See, e.g., id.* at 71:22-72:3.) Also, the only challenge Sun submits to Dr. Davies' testimony regarding the nexus between patient preference and the asserted claims is Mr. Fischer's 2013 article indicating that the improved taste may be attributed to excipients that are not claimed. (*Id.* at 118:18-23.) Even if the Court were to accept Sun's position and find no nexus between improved taste and the asserted claims, Sun has provided no evidence to dispute Dr. Davies' testimony regarding the nexus between patient preference and improved dissolution time and claim 2 of the '900 patent and the '387 patent requiring a superdisintegrant. Therefore, the Court finds the unexpected patient preference supports non-obviousness of the asserted claims.

c. Industry Praise

Finally, Orexo argues that industry praise for Zubsolv® supports non-obviousness of the asserted claims. (Davies Tr. 1136:14-24.) Orexo relies on an article titled "Buprenorphine/Naloxone (Zubsolv®): A Review in Opioid Dependence" ("Heo") written by Young-A Heo that praised Zubsolv® for higher bioavailability, better taste, and faster sublingual dissolve time which led to greater patient preference. (PTX- 0157.0001.) Heo's article was peer reviewed by G.E. Woody from the Department of Psychiatry at the Perelman School of Medicine,

University of Pennsylvania, and M Lapeyre-Mestre from the Department of Clinical and Medical Pharmacology at the University of Toulouse III, Toulouse, France. (*Id.*) Orexo also cites to an article titled, "Buprenorphine and its formulations: a comprehensive review," published in the journal *Health Psychology Research* and written by authors employed at hospitals and medical schools ("Poliwoda"). (PTX-0420.) Poliwoda praises Zubsolv® because "the film formulation of Suboxone® is generally harder for patients to take and more of an unpleasant tangy taste in the mouth. In contrast, Zubsolv® has better bioavailability and is offered in wider doses." (*Id.* at 0420.0005.) Dr. Davies testified that there is a nexus between industry praise and the claims because the industry praise arises from the improved bioavailability, which is a feature of the structural elements of the asserted claims. (Davies Tr. 1164:9-1165:1.)

Sun contends that Orexo's evidence of industry praise is insufficient because "there was nothing in Heo that was novel. It was a review article of a very limited set" and the statement in Poliwoda regarding Zubsolv® having greater bioavailability is unclear about whether it is comparing Suboxone® film to Suboxone® tablets, Zubsolv® tablets, or both, and that the sentence is a just a statement of fact and not praise. (Wexler Tr. 164:11-165:2, 178:15-179:21.) Dr. Wexler testified that he has never heard of others in the field praising Zubsolv® alone or compared to Suboxone®. (*Id.* at 171:20-24.)

The Court does not find Dr. Wexler's testimony in this regard credible as Heo is peer-reviewed and refers to twenty different references and the Court's reading of Poliwoda is suggestive of industry praise rather than a statement of fact. Furthermore, Sun's own witness noted that "no one had developed a new sublingual tablet with the same level of enhanced bioavailability compared to Suboxone® tablets before Orexo." (Crowley Tr. 1086:7-10.) Dr. Crowley testified that Zubsolv® has "improved bioavailability compared to Suboxone® tablets" and that

"improving the bioavailability for a known active ingredient with a new formulation is generally a benefit[.]" (*Id.* at 1086:11-1087:3.)

As such, the Court finds that sufficient evidence exists that people in the industry praised Zubsolv® for its improved bioavailability, which as Dr. Davies testified to is a feature of the structural elements of the asserted claims. Therefore, the Court finds industry praise for Zubsolv® supports non-obviousness of the asserted claims.

In sum, the secondary considerations support a finding that the asserted claims and were not obvious. In conclusion, for the reasons stated above, Sun fails to prove obviousness by clear and convincing evidence. *Procter & Gamble*, 566 F.3d 994 (noting that obviousness must be proven by clear and convincing evidence).

III. CONCLUSION

For the reasons stated herein, the Court finds that Sun's ANDA Products **INFRINGE** upon the '900 and '387 patents, and that the '900 and '387 patents are **VALID**. An appropriate Order will follow.

Dated: June 30, 2023

GEORGETTE CASTNER
UNITED STATES DISTRICT JUDGE